communities. If the screening interval can be extended, endoscopic screening may be used efficiently even with limited resources.

A notable constraint of the present study is the lack of data regarding the clinical stage of the interval cancer. To evaluate the effects of interval cancer, follow-up of the participants of a population-based screening based on the cancer registry is needed. In Japan, cancer registries have not yet been prepared at the national level, and the registry method has not yet been standardized as of 2014 [23, 24]. The Tottori Cancer Registry is one of the most reliable systems with a long history in Japan. Although information about disease extension has been obtained as an alternative item for the clinical stage, this information is often lacking [25]. The quality of the Tottori Cancer Registry was, however, not optimal since the percentage of death-certification-only cases was 15.1% in 2007 which was lower than the national average [26]. Even if there was a notification of new cases in the cancer registration system, detailed information was often lacking because the clinical stage was not a necessary item. Fortunately, additional information could be obtained for the screening group from the Tottori Medical Association database because the association has the responsibility of implementing gastric cancer screening programs and collecting detailed information for quality assurance. However, we could not obtain additional detailed information regarding the numbers of medical institutions in Tottori Prefecture for the outpatient group and the interval cancer cases in both screening groups. These limitations prevented us from obtaining stage information sufficiently, thus careful interpretation of the results in reference to these contains is required.

This study has other limitations. First, the background difference should be considered between the endoscopic screening group and the radiographic screening group. Endoscopic screening has been performed in clinical practice in Tottori Prefecture. The age of the participants in endoscopic screening was more advanced than that of the participants in radiographic screening [7]. Individuals aged more than 70 years could be screened by physicians using endoscopy in their own private practice. Since younger people who have family physicians were fewer than older people who have family physicians, there was little opportunity for the younger people to be tested in clinical practice. Second, since there was no information as to whether or not the patients participated in opportunistic screenings, the outpatient group might include cancer patients which were detected by these screenings. Selection bias may also be considered in the selection of the screening method at the individual level. Third, the survival rate was different among hospitals in Japan [27]. Moreover, the present results are limited to local areas in Japan. Finally, subgroup analysis could not be adequately performed because of the small sample size.

In conclusion, the gastric cancer-specific and all-causes survival rates of patients with screen-detected cancers and patients with interval cancers were nearly equal in the annual endoscopic screening. The risk of gastric cancer death was lower in the patients with screen-detected and interval cancers in the endoscopic screening group than in the outpatient group. These results suggest the potential of endoscopic screening in reducing mortality from gastric cancer. However, additional studies must be performed to more extensively evaluate mortality reduction from gastric cancer by endoscopic screening as well as to investigate the impact of interval cancer on the effectiveness of endoscopic screening for gastric cancer.

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Author Contributions

Conceived and designed the experiments: CH TK. Performed the experiments: MS MO YO. Analyzed the data: CH TK. Contributed reagents/materials/analysis tools: CH MS. Wrote the paper: CH TK.

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SPECIAL REPORT

Breast-Cancer Screening — Viewpoint of the IARC Working Group

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In November 2014, experts from 16 countries met at the International Agency for Research on Cancer (IARC) to assess the cancer-preventive and adverse effects of different methods of screening for breast cancer. (The members of the working group for volume 15 of the IARC Handbook are listed at the end of the article; affiliations are provided in the Supplementary Appendix, available with the full text of this article at NEJM.org.) This update of the 2002 IARC handbook on breast-cancer screening[1] is timely for several reasons. Recent improvements in treatment outcomes for late-stage breast cancer and concerns regarding overdiagnosis call for reconsideration. The definition of what constitutes the best implementation of mammographic screening programs (e.g., which age groups should be screened and with what frequency) needs to be revisited in light of the results of recent studies. New studies on clinical breast examination and self-examination warrant the reevaluation of these screening practices, and imaging techniques other than mammography, which were not evaluated in the 2002 handbook, now warrant rigorous scientific evaluation. Finally, the screening of women at high risk for breast cancer requires a thorough reassessment, particularly in the context of the improved data that are now available on possible alternative screening methods.

In preparation for the meeting, the IARC scientific staff performed searches of the openly available scientific literature according to topics listed in an agreed-upon table of contents; searches were supplemented by members of the working group on the basis of their areas of expertise. Group chairs and subgroup members were selected by the IARC according to field of expertise and the absence of real or apparent conflicts of interest. During the meeting, care was taken to ensure that each study summary was written or reviewed by someone who was not associated with the study being considered. All studies were assessed and fully debated, and a consensus on the preliminary evaluations was achieved in subgroups before the evaluations were reviewed by the entire working group. During the final evaluation process, the working group discussed preliminary evaluations to reach consensus evaluations. (For details on the process used and on the evaluation criteria, see the working procedures on the IARC handbooks website.[2]) This article briefly summarizes the evaluation of the scientific evidence reviewed at the meeting (Table 1). The full report is presented in volume 15 of the IARC Handbooks of Cancer Prevention.[3]

Breast cancer is the most frequently diagnosed cause of death from cancer in women worldwide,[4,5] the second leading cause of death from cancer in women in developed countries,[4,5] and the leading cause of death from cancer in low- and middle-income countries, where a high proportion of women present with advanced disease, which leads to a poor prognosis.[6] Established risk factors for breast cancer include age, family or personal history of breast cancer or of precancerous lesions, reproductive factors, hormonal treatment, alcohol consumption, obesity (for postmenopausal breast cancer only), exposure to ionizing radiation, and genetic predisposition.[7]

Screening for breast cancer aims to reduce mortality from this cancer, as well as the morbidity associated with advanced stages of the disease, through early detection in asymptomatic women. The key to achieving the greatest potential effects from this screening is providing early access to effective diagnostic and treatment services. Comprehensive quality assurance is essential to maintaining an appropriate balance between benefits and harms.[8]

Table 1. Evaluation of Evidence Regarding the Beneficial and Adverse Effects of Different Methods of Screening for Breast Cancer in the General Population and in High-Risk Women.*

Method	Strength of Evidence†
Mammography	
Reduces breast-cancer mortality in women 50–69 yr of age	Sufficient
Reduces breast-cancer mortality in women 70–74 yr of age‡	Sufficient
Reduces breast-cancer mortality in women 40–44 yr of age§	Limited
Reduces breast-cancer mortality in women 45–49 yr of age§	Limited¶
Detects breast cancers that would never have been diagnosed or never have caused harm if women had not been screened (overdiagnosis)	Sufficient
Reduces breast-cancer mortality in women 50–74 yr of age to an extent that its benefits substantially outweigh the risk of radiation-induced cancer from mammography	Sufficient
Produces short-term negative psychological consequences when the result is false positive	Sufficient
Has a net benefit for women 50–69 yr of age who are invited to attend organized mammographic screening programs	Sufficient
Can be cost-effective among women 50–69 yr of age in countries with a high incidence of breast cancer	Sufficient
Can be cost-effective in low- and middle-income countries	Limited
Ultrasonography as an adjunct to mammography in women with dense breasts and negative results on mammography	
Reduces breast-cancer mortality	Inadequate
Increases the breast-cancer detection rate	Limited
Reduces the rate of interval cancer‖	Inadequate
Increases the proportion of false positive screening outcomes	Sufficient
Mammography with tomosynthesis vs. mammography alone	
Reduces breast-cancer mortality	Inadequate
Increases the detection rate of in situ and invasive cancers	Sufficient
Preferentially increases the detection of invasive cancers	Limited
Reduces the rate of interval cancer‖	Inadequate
Reduces the proportion of false positive screening outcomes	Limited
Clinical breast examination	
Reduces breast-cancer mortality	Inadequate
Shifts the stage distribution of tumors detected toward a lower stage	Sufficient
Breast self-examination	
Reduces breast-cancer mortality when taught	Inadequate
Reduces the rate of interval cancer when taught‖	Inadequate
Reduces breast-cancer mortality when practiced competently and regularly	Inadequate
Screening of high-risk women	
MRI as an adjunct to mammography	
Reduces breast-cancer mortality in women with a *BRCA1* or *BRCA2* mutation	Inadequate
Increases the detection rate of breast cancer in women with lobular carcinoma in situ or atypical proliferations	Inadequate
Clinical breast examination as an adjunct to MRI and mammography	
Increases the detection rate of breast cancer in women with a high familial risk	Inadequate
Ultrasonography as an adjunct to mammography	
Increases the detection rate of breast cancer in women with a personal history of breast cancer	Inadequate
Increases the proportion of false positive screening outcomes in women with a personal history of breast cancer as compared with those without such a history	Inadequate
MRI as an adjunct to mammography plus ultrasonography	

Table 1. (Continued.)

Method	Strength of Evidence†
Increases the proportion of false positive screening outcomes in women with a personal history of breast cancer as compared with those without such a history	Inadequate
MRI as an adjunct to mammography vs. mammography alone	
Increases the proportion of false positive screening outcomes in women with lobular carcinoma in situ or atypical proliferations	Limited

* For the complete evaluation statements, see International Agency for Research on Cancer[2] or the IARC Handbooks of Cancer Prevention website (http://handbooks.iarc.fr). MRI denotes magnetic resonance imaging.
† For detailed information on the evaluation criteria, see the working procedures section of the IARC Handbooks of Cancer Prevention website (http://handbooks.iarc.fr/workingprocedures/index.php).
‡ The evidence for a reduction in breast-cancer mortality from mammography screening in women in this age group was considered to be sufficient. However, published data for this age category did not allow for the evaluation of the net benefit.
§ The evidence for a reduction of breast-cancer mortality from mammography screening in women in this age group was considered to be limited. Consequently, the net benefit for women in this age group was not assessed.
¶ The majority of the voting members of the IARC Working Group considered the evidence as limited; however, the vote was almost evenly divided between limited and sufficient evidence.
‖ An interval cancer is a cancer that develops in the interval between routine screenings for that particular cancer.

The most common means of screening women for breast cancer is standard mammography (film or digital), offered either by organized programs or through opportunistic screening. Organized screening programs are characterized by invitations to join a target population at given intervals, systematic recalls for the assessment of detected abnormalities, and delivery of test results, treatment, and follow-up care, with regular monitoring and evaluation of the program and a national or regional team responsible for service delivery and quality. Opportunistic screening typically provides screening to women on request and coincidently with routine health care.

As a consequence of the results of randomized, controlled trials that showed a reduction in breast-cancer mortality several decades ago,[1] mammographic screening has been implemented to a great extent in high-income countries and regions and less so in countries in Central and Eastern Europe, through either opportunistic or organized screening. Most countries in Latin America have national recommendations or guidelines, including those calling for mammographic screening combined with clinical breast examination and breast self-examination. In other low- and middle-income countries, breast-cancer screening is promoted primarily by advocacy groups and periodic campaigns to promote breast-cancer awareness.

In 2002, on the basis of findings from randomized, controlled trials, the previous IARC Handbook Working Group concluded that the evidence for the "efficacy of screening by mammography as the sole means of screening in reducing mortality from breast cancer" was sufficient for women 50 to 69 years of age, limited for women 40 to 49 years of age, and inadequate for women younger than 40 or older than 69 years of age.[1] We carefully reviewed the results of all available randomized, controlled trials and reaffirmed the findings from the previous evaluation of the efficacy of mammographic screening in women 50 to 69 years of age; the evidence of efficacy for women in other age groups was considered inadequate.

The working group recognized that the relevance of randomized, controlled trials conducted more than 20 years ago should be questioned, given the large-scale improvements since then in both mammographic equipment and treatments for breast cancer. More recent, high-quality observational studies were considered to provide the most robust data with which to evaluate the effectiveness of mammographic screening. The working group gave the greatest weight to cohort studies with long follow-up periods and the most robust designs, which included those that accounted for lead time, minimized temporal and geographic differences between screened and unscreened participants, and controlled for individual differences that may have been related to the primary outcome. Analyses of invitations to screenings (rather than actual attendance) were

considered to provide the strongest evidence of screening effectiveness, since they approximate the circumstances of an intention-to-treat analysis in a trial. After careful consideration of the limitations of case–control studies in the evaluation of effectiveness, these studies were also considered to provide information that was relevant to organized screening programs and to other venues, such as opportunistic screening, for which cohort data were not available. Among ecologic studies, only those that controlled for time- and treatment-related factors in design or analysis were considered to be informative.

Some 20 cohort and 20 case–control studies, all conducted in the developed world (Australia, Canada, Europe, or the United States) were considered to be informative for evaluating the effectiveness of mammographic screening programs, according to invitation or actual attendance, mostly at 2-year intervals. Most incidence-based cohort mortality studies, whether involving women invited to attend screening[9-13] or women who attended screening,[14-17] reported a clear reduction in breast-cancer mortality, although some estimates pertaining to women invited to attend were not statistically significant.[12,13] Women 50 to 69 years of age who were invited to attend mammographic screening had, on average, a 23% reduction in the risk of death from breast cancer; women who attended mammographic screening had a higher reduction in risk, estimated at about 40%. Case–control studies that provided analyses according to invitation to screening were largely in agreement with these results. Evidence from the small number of informative ecologic studies was largely consistent with that from cohort and case–control studies. A substantial reduction in the risk of death from breast cancer was also consistently observed in women 70 to 74 years of age who were invited to or who attended mammographic screening in several incidence-based cohort mortality studies.[17-19] Fewer studies assessed the effectiveness of screening in women 40 to 44 or 45 to 49 years of age who were invited to attend or who attended mammographic screening, and the reduction in risk in these studies was generally less pronounced.[20-23] Overall, the available data did not allow for establishment of the most appropriate screening interval.

The most important harms associated with early detection of breast cancer through mammographic screening are false positive results, overdiagnosis, and possibly radiation-induced cancer. Estimates of the cumulative risk of false positive results differ between organized programs and opportunistic screening. The estimate of the cumulative risk for organized programs is about 20% for a woman who had 10 screens between the ages of 50 and 70 years.[24] Less than 5% of all false positive screens resulted in an invasive procedure. Owing to differences in health systems and quality control for screening performance, recall rates for additional investigation tend to be higher in opportunistic screening (e.g., in the United States)[25] than in organized screening programs. Overall, studies show that having a false positive mammogram has short-term negative psychological consequences for some women.[26]

Overdiagnosis can be estimated on the basis of data from observational studies conducted in organized programs or through statistical modeling. There is an ongoing debate about the preferred method for estimating overdiagnosis. After a thorough review of the available literature, the working group concluded that the most appropriate estimation of overdiagnosis is represented by the difference in the cumulative probabilities of breast-cancer detection in screened and unscreened women, after allowing for sufficient lead time. The Euroscreen Working Group calculated a summary estimate of overdiagnosis of 6.5% (range, 1 to 10%) on the basis of data from studies in Europe that adjusted for both lead time and contemporaneous trends in incidence.[27,28] When the same comparators were used, corresponding estimates of overdiagnosis in randomized, controlled trials after a long follow-up period from the end of screening were similar (4 to 11%).[29,30] Similar non-European and more recent European observational studies have led to higher estimates of overdiagnosis.

Radiation-induced breast cancer is a concern in women who are offered screening. The estimated cumulative risk of death from breast cancer due to radiation from mammographic screening is 1 to 10 per 100,000 women, depending on age and the frequency and duration of screening. It is smaller by a factor of at least 100 than the estimates of death from breast cancer that are prevented by mammographic screening for a wide range of ages.[31]

After a careful evaluation of the balance be-

tween the benefits and adverse effects of mammographic screening, the working group concluded that there is a net benefit from inviting women 50 to 69 years of age to receive screening. A number of other imaging techniques have been developed for diagnosis, some of which are under investigation for screening. Tomosynthesis, magnetic resonance imaging (MRI) (with or without the administration of contrast material), ultrasonography (handheld or automated), positron-emission tomography, and positron-emission mammography have been or are being investigated for their value as supplementary methods for screening the general population or high-risk women in particular.

Evidence for population screening with other imaging techniques is based solely on data from observational studies. The use of adjunct ultrasonography in women with dense breasts and negative results on mammography may increase the detection rate of cancers, but it also increases false positive screening outcomes.[32] As compared with mammography alone, mammography with tomosynthesis increases rates of detection of both in situ and invasive cancers and may reduce false positive screening outcomes[33]; however, evidence for a reduction in breast-cancer mortality was inadequate (Table 1) and the radiation dose received with dual acquisition is increased.

Clinical breast examination is a simple, inexpensive technique. In three trials in which women were randomly assigned to receive either clinical breast examination or no screening, breast cancers detected at baseline and in the early years of the trials tended to be of a smaller size and less advanced stage in the former group of women than in the latter.[34-36] Results on breast-cancer mortality have not yet been reported. In addition, five observational studies, conducted mostly in the 1970s, reported that clinical breast examination combined with mammographic screening increased the breast-cancer detection rate by 5 to 10 percentage points as compared with mammography alone.[1]

As has been previously reported,[1] the available data from randomized, controlled trials and observational studies generally did not show a reduction in breast-cancer mortality when breast self-examination was either taught or practiced competently and regularly (Table 1). Overall, surveys in general populations have shown that the numbers of women who report practicing breast self-examination are probably too few to have had an effect on mortality from breast cancer.

Women with a family history of breast cancer, with or without a known genetic predisposition, are at increased risk for breast cancer and therefore may benefit from intensified monitoring, with a combination of methods, from an earlier age and possibly at shorter intervals than women at average risk. However, high-risk women may be more sensitive to ionizing radiation,[37] and screening from an earlier age increases the risk of radiation-induced cancer. A number of observational studies have evaluated the sensitivity, specificity, incremental rate of breast-cancer detection, and false positive outcomes associated with various imaging techniques in high-risk women (Table 1). There is abundant literature showing that the use of MRI as an adjunct to mammography significantly increases the sensitivity of screening in women with a high familial risk and a *BRCA1* or *BCRA2* mutation as compared with mammography alone, but the addition of MRI also decreases the specificity[38]; data for other high-risk groups were fewer and provided weaker evidence.[39] The sensitivity of ultrasonography was found to be similar to or lower than that of mammography and was consistently lower than that of MRI.[40] The evidence regarding other screening techniques was too sparse to allow any conclusions.

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Review Article

A meta-analysis of mammographic screening with and without clinical breast examination

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Mammographic screening with clinical breast examination has been recommended in Japan since 2000. Although mammographic screening without clinical breast examination has not been recommended, its introduction is anticipated. The efficacies of mammographic screening with and without clinical breast examination were evaluated based on the results of randomized controlled trials. PubMed and other databases for studies published between 1985 and 2014 were searched. The study design was limited to randomized controlled trials to evaluate mortality reduction from breast cancer. Five studies were eligible for meta-analysis of mammographic screening without clinical breast examination. The relative risk for women aged 40–74 years was 0.75 (95% confidence interval, 0.67–0.83). Three studies evaluated the efficacy of mammographic screening with clinical breast examination. The relative risk for women aged 40–64 years was 0.87 (95% confidence interval, 0.77–0.98). The number needed to invite was always lower in mammographic screening without clinical breast examination than in mammographic screening with clinical breast examination. In both screening methods, the number needed to invite was higher in women aged 40–49 years than in women aged 50–70 years. These results suggest that mammographic screening without clinical breast examination can afford higher benefits to women aged 50 years and over. Although evidence of the efficacy of mammographic screening without clinical breast examination was confirmed based on the results of the randomized controlled trials, a Japanese study is needed to resolve local problems.

Breast cancer is currently the most common cancer in Japan and accounts for 19.0% of all new cancers.[1] The age-standardized rate has been reported to be 51.5 per 100 000 women. The incidence rate of breast cancer initially increased gradually between 1975 and 1999 and has risen steeply since 2000 when mammography was introduced for breast cancer screening. In North America and Europe, the incidence of breast cancer has increased according to age. In Japan, the highest incidence rate of breast cancer has been observed in women aged 45–49 years.[1]

Japan is the first among East Asian countries to introduce breast cancer screening, and it has a unique program for population-based screening. In 1987, the Japanese government approved the introduction of breast cancer screening in Japan.[2] The first screening method was clinical breast examination with women aged 30 years and over as the target population. In 2000, mammographic screening was added for women aged 50 years and over, but clinical breast examination was used for women aged 30–49 years. Since 2004, a combination of mammography and clinical breast examination has been recommended for women aged 40 years and over as population-based screening. However, in most developed countries, mammographic screening without clinical breast examination has been the standard method for breast cancer screening. In the previous evidence report for cancer screening in Japan, it was not clearly specified why mammographic screening without clinical breast examination is not recommended.[3] Although mammographic screening without clinical breast examination has not been recommended, its introduction to local communities is anticipated owing to limitations in specialists who can carry out clinical breast examination. To successfully introduce mammographic screening without clinical breast examination, the efficacy of mammography must be evaluated with and without clinical breast examination. However, most guidelines and evidence reports have combined the results of a meta-analysis for mammographic screening with and without clinical breast examina-

tion.[4,5] There has been a lengthy discussion regarding the appropriateness of including women aged 40–49 years in the target population for breast cancer screening.[4,5] In most European countries, the target age group is 50–69 years, excluding the 40–49 years age group.[6]

To confirm evidence of the effectiveness of the Japanese screening program and to identify the best available method for breast cancer screening in Japan, we carried out a systematic review and meta-analysis of randomized controlled trials (RCTs) with and without mammographic screening. The results of the systematic review and meta-analysis were used for the development of comprehensive guidelines for breast cancer screening published by the National Cancer Center, Japan.

Methods

Systematic review of published reports. To identify the individual efficacy of mammographic screening with and without clinical breast examination, we searched PubMed, Web of Science, Igaku-Cyuo zasshi, and J Dream databases for studies using search terms such as "breast cancer", "mammography", "clinical breast examination", "physical breast examination", or "mortality reduction", published between January 1985 and April 2012. Additional references recommended were identified and included as needed. If the result from a branch of a large-scale RCT was published, the study was included. In addition, we searched for articles with revised results based on an extended follow-up and other RCTs regarding mammographic screening to evaluate mortality reduction from breast cancer from April 2012 to December 2014. The searches were limited to English language or Japanese language publications. Original articles published after peer review were included, whereas guidelines and evidence reports were excluded. The study design was limited to RCTs to evaluate mortality reduction from breast cancer. Modeling studies were not included. The RCTs for mammographic screening with and without clinical breast examination compared with a no screening group with the usual care were selected.

To select appropriate evidence for our research questions, we carried out a two-stage review: the title and abstract were initially checked and the full papers were subsequently reviewed. For the initial step, articles without an abstract were also excluded. Two reviewers screened the abstracts individually and subsequently reviewed the full papers of potentially relevant studies. To select appropriate evidence, a systematic review of the retrieved articles was carried out using the checklist according to the study design and the quality of the studies was defined.[7] If the decision for the full paper review was inconsistent, the appropriateness of these studies was carefully discussed. Finally, adequate studies were selected and included in a meta-analysis.

Meta-analysis. Based on the results of the systematic review, we carried out a meta-analysis. Although the follow-up years were different among the studies, we cited the results of 13 years follow-up from the Cochrane review[8] and original data from selected articles. Meta-analysis for RCTs of mammography with and without clinical breast examination was carried out for women of different age groups as follows: women aged 40–74 years (all age group), women aged 40–49 years, and women aged 50 years and over. For studies that reported cumulative count data, we carried out a Mantel–Haenszel fixed-effects meta-analysis to obtain the relative risk with the corresponding 95% confidence interval (CI). Statistical analyses were carried out using StatsDirect3 (StatsDirect, Altrincham, UK).

Comparison of benefit and harm. To compare benefit and harm, the number needed to invite (NNI) was calculated on the basis of the mortality risk from breast cancer in Japanese women. The NNI refers to the number needed to avoid one breast cancer death. The NNI can show the impact of the benefits of cancer screening, as well as suggest harms because unnecessary examinations increase with increasing number. To estimate the NNI in Japan, we used the prediction results for Japanese women[9] and the meta-analysis results.

A high recall rate for diagnostic examination can also be considered as harm for mammographic screening participants owing to an increase in unnecessary examinations. We also calculated the number needed for diagnostic examination to avoid one breast cancer death on the basis of the recall rate of mammographic screening in communities.[10] These results were compared between mammographic screening with and without clinical breast examination divided into different age groups from 40 to 70 years.

Results

Search of published works. The number of articles identified from the search using PubMed and other databases was 5270. After a two-stage review, 110 English articles were selected. From these 110 articles, six RCTs for mammographic screening without clinical breast examination were identified: Malmö study,[11,12] Canadian study II,[13–15] Swedish Two-County study,[16–22] Stockholm study,[23,24] Gothenburg study,[25,26] and the UK Age trial.[27] Three RCTs for mammographic screening with clinical breast examination were also identified as follows: New York HIP study,[28] Edinburgh study,[29] and Canadian study I.[30,31] The Canadian studies consisted of two groups with different targets: women aged 50–59 years for Canadian study II,[13–15] and women aged 40–49 years for Canadian study I.[30,31] In Canadian study II, the screening method for the intervention group was mammography with clinical breast examination; clinical breast examination was also provided for the control group with the same frequency as that for the intervention group.[13–15] In Canadian study I, the screening method for the intervention group was mammography with clinical breast examination; clinical breast examination was provided for the control group only at the first screening.[30,31] Based on the inclusion criteria related to a comparator, we excluded Canadian study II from the evidence of mammography without clinical breast examination, and included Canadian study I as the evidence of mammography with clinical breast examination. From April 2012 to December 2014, although the revised results were reported in a Canadian study, there were no additional studies to evaluate mortality reduction from breast cancer.[15]

Evidence of mammographic screening with and without clinical breast examination. *Mammographic screening without clinical breast examination.* Five RCTs of mammographic screening without clinical breast examination were identified for mortality reduction from breast cancer (Table 1).[11–27] Each of these studies began in the 1980s, except the UK Age trial which started in 1991. Randomized allocation was performed at individual base except the Swedish Two-County study. Although the screening method was the same in these studies, the target age group, screening interval, and follow-up periods were different (Table 1). Although the target age group was different among the five RCTs, all of these studies included women aged in their

Table 1. Randomized controlled trials for evaluation of mammographic screening without clinical breast examination

	Malmö I and II	Swedish Two-County	Stockholm	Gothenburg	UK Age trial
Starting year of the study	1976	1977	1981	1982	1991
Randomization	Individual	Cluster	Birthday	Birthday	Individual
Number	60 076	133 065	60 800	52 222	160 921
Target age	45–69 years/43–49 years	38–75 years	39–65 years	39–59 years	39–41 years
Screening method	MMG	MMG+SBE	MMG	MMG	MMG
View	First, two-view Subsequent, one-view or two-view	One-view	One-view	First, two-view Subsequent, one-view or two-view	First, two-view Subsequent, one-view or two-view
Screening interval, months	18–24	24 (40s)–33 (50s)	24–28	18	12
Screening frequency	6–8	2–4	2	4–5	8–10
Screening periods, years	12	7	4	7	8
Participation rate, %	74	85	82	84	81
Relative risk (95%CI)	0.81 (0.61–1.07)	0.68 (0.57–0.81)	0.73 (0.50–1.06)	0.75 (0.58–0.97)	0.83 (0.66–1.04)

Relative risk was based on the results of 13 years of follow-up based on the references 8 (Gøtzsche & Jørgensen, 2013) and 16 (Tabar *et al.*, 1995). CI, confidence interval; MMG, mammography; SBE; self-breast examination.

40s as their target age group. In the UK Age trial, the study targets were limited to women aged 39–41 years years because the aim of the trial was evaluation of the efficacy of mammography for women aged in their 40s.[27] The screening view was mainly one-view, but two-view was used at the first screening in the Malmö study, Gothenburg study, and UK Age trial. The screening interval for women aged 50 years and over was from 18 to 33 months. The results were analyzed using the intention to treat method in all studies.

Based on the outcome of 13 years of follow-up, the results suggest mortality reduction from breast cancer by mammographic screening without clinical breast examination, although significant results were also obtained in the Swedish Two-County study (0.68; 95%CI, 0.57–0.81) and Gothenburg study (0.75; 95%CI, 0.58–0.97).[10] When the targets of these studies were limited to women aged in their 40s, significant results in terms of mortality reduction from breast cancer could not be obtained in all the studies.

Mammographic screening with clinical breast examination. Three RCTs of mammographic screening with clinical breast examination served as eligible evidence for mortality reduction from breast cancer (Table 2).[28–31] Compared with the studies related to mammographic screening without clinical breast examination, the starting years of these studies were early and detailed information was insufficient. The New York HIP study was the first RCT of this kind. It started in 1963 with the aim of evaluating the efficacy of mammographic screening.[28] The other studies commenced around the 1980s. In the Edinburgh study, inappropriate randomization was suggested because of the different socio-economic classes between the intervention group and the control group.[29] Although the screening method was the same in these studies, the control group in Canadian study I was initially provided clinical breast screening.[30,31] Although the target age group was different among the three RCTs, all of these studies included women aged 40s as their target. Although two-view mammography was used for all the studies, the screening interval was different, that is, 12 months for the New York HIP study[28] and Canadian study I,[30,31] and 24 months for the Edinburgh study.[29] The results were analyzed using the intention to treat method. The results of 13 years of follow-up for the New York HIP study and Canadian study I were obtained from the Cochrane review.[8] The results of 14 years of follow-up for

Table 2. Randomized controlled trials for evaluation of mammographic screening with physical examination

	New York HIP	Canada I	Edinburgh
Starting year of study	1963	1980	1978
Randomization Subjects	Individual	Individual	Cluster
Number	62 000	89 835	54 654
Target age	40–64 years	40–49 years	45–64 years
Screening method	MMG+CBE	MMG+CBE+SBE	MMG+CBE
Mammography View	Two-view	Two-view	First, two-view Subsequent, one-view or two-view
Screening interval, months	12	12	24
Screening frequency	4	4–5	2–4
Screening periods, years	3	5	6
Participation rate, %	65	88	65
Relative risk (95%CI)	0.83 (0.70–0.99)	0.97 (0.74–1.27)	0.85 (0.68–1.05)

Relative risk was based on the results of 13 years of follow-up for the New York HIP and Canada I studies (Gøtzsche & Jørgensen, 2013), and 14 years of follow-up for the Edinburgh study (Alexander *et al.*, 1999). CBE, clinical breast examination; CI, confidence interval; MMG, mammography; SBE, self breast examination.

the Edinburgh study[29] were directly obtained from the article. Although not statistically significant, these results suggest mortality reduction from breast cancer by mammographic screening with clinical breast examination. Similar results were suggested when the targets of these studies were limited to women aged 40–49 years.

Meta-analysis. *Mammographic screening without clinical breast examination.* Five studies were eligible for the meta-analysis of mammographic screening without clinical breast examination programs (Table 1). The overall relative risk for all the age groups was 0.75 (95%CI, 0.67–0.83) (Fig. 1a). When the target age group was divided into two groups, the relative risks were 0.81 (95%CI, 0.68–0.96) for women aged 40–49 years and 0.71 (95%CI, 0.62–0.81) for women aged 50–74 years (Fig. 1b,c).

Mammographic screening with clinical breast examination. Three studies were selected to evaluate the efficacy of mammographic screening with clinical breast examination (Table 2). The overall relative risk for all the age groups was 0.87 (95%CI, 0.77–0.98) (Fig. 2a). When the target age group was divided into two groups, the relative risks were 0.87 (95% CI, 0.72–1.04) for women aged 40–49 years and 0.83 (95%CI, 0.70–0.99) for women aged 50–64 years (Fig. 2b,c).

Comparison of benefit and harm. The NNI and the number needed for diagnostic examination to avoid one breast cancer death were calculated for mammographic screening with and without clinical breast examination for women aged 40–70 years (Table 3). The NNI was consistently lower in mammographic screening without clinical breast examination than in mammographic screening with clinical breast examination. In both screening methods, the NNI was higher in women aged 40–49 years than in women aged 50–70 years. Similar results were obtained for the number needed for recall of diagnostic examination to avoid one breast cancer death. These results suggest that mammographic screening without clinical breast examination could provide higher benefits for women aged 50 years and over.

Discussion

Although it has been 15 years since the Japanese government has recommended mammographic screening with clinical breast examination, mammographic screening without clinical breast examination has not yet been introduced. In the present study, individual efficacy could be confirmed for mammographic screening with and without clinical examination. The impacts of mortality reduction were different between both methods. The NNIs of mammographic screening without clinical breast examination were consistently lower than those of mammographic screening with clinical breast examination among women aged 40–70 years. In addition, the recall rate for diagnostic examinations was higher in mammographic screening with clinical breast examination than in mammographic screening without clinical breast examination.[10] Compared with mammographic screening with clinical breast examination, mammographic screening without clinical breast examination could reduce harm. However, the NNIs were always higher in women aged 40–49 years than in women aged 50 years and over for both methods.

Clinical breast examination was introduced as the first screening method for breast cancer and it has been carried out with mammographic screening in Japan.[2] In Japan, physicians perform clinical breast examinations, whereas in some countries, nurses can undertake that role. In the Canadian I and II studies, clinical breast examinations were carried out by trained nurses.[13–15,30,31] The Edinburgh study also recommended clinical breast examinations be carried out by nurses.[29] Although clinical breast examination alone was not

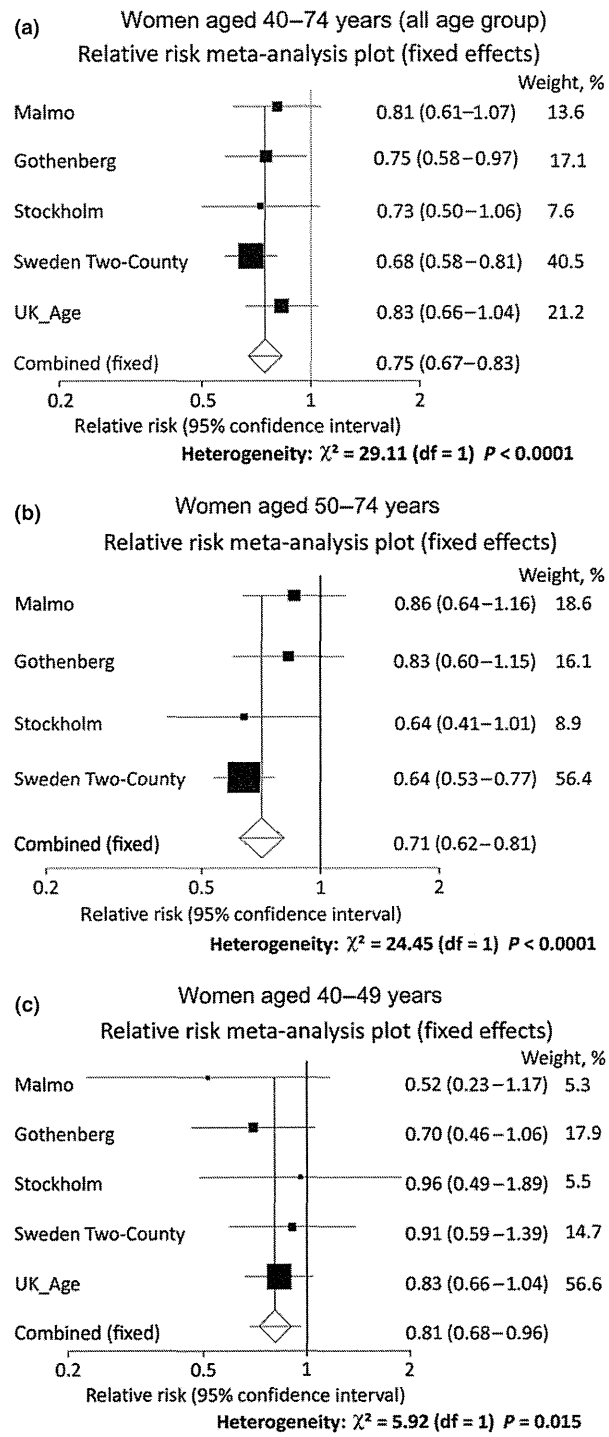

Fig. 1. Meta-analysis of mammography without clinical breast examination. Five studies were eligible for the meta-analysis of mammographic screening without clinical breast examination programs: Malmö study,[11,12] Swedish Two-County study,[16–22] Stockholm study,[23,24] Gothenburg study,[25,26] and UK Age trial.[27] Women were divided into three target age groups: 40–74 years (all age group) (a); 50–74 years (b); 40–49 years (c).

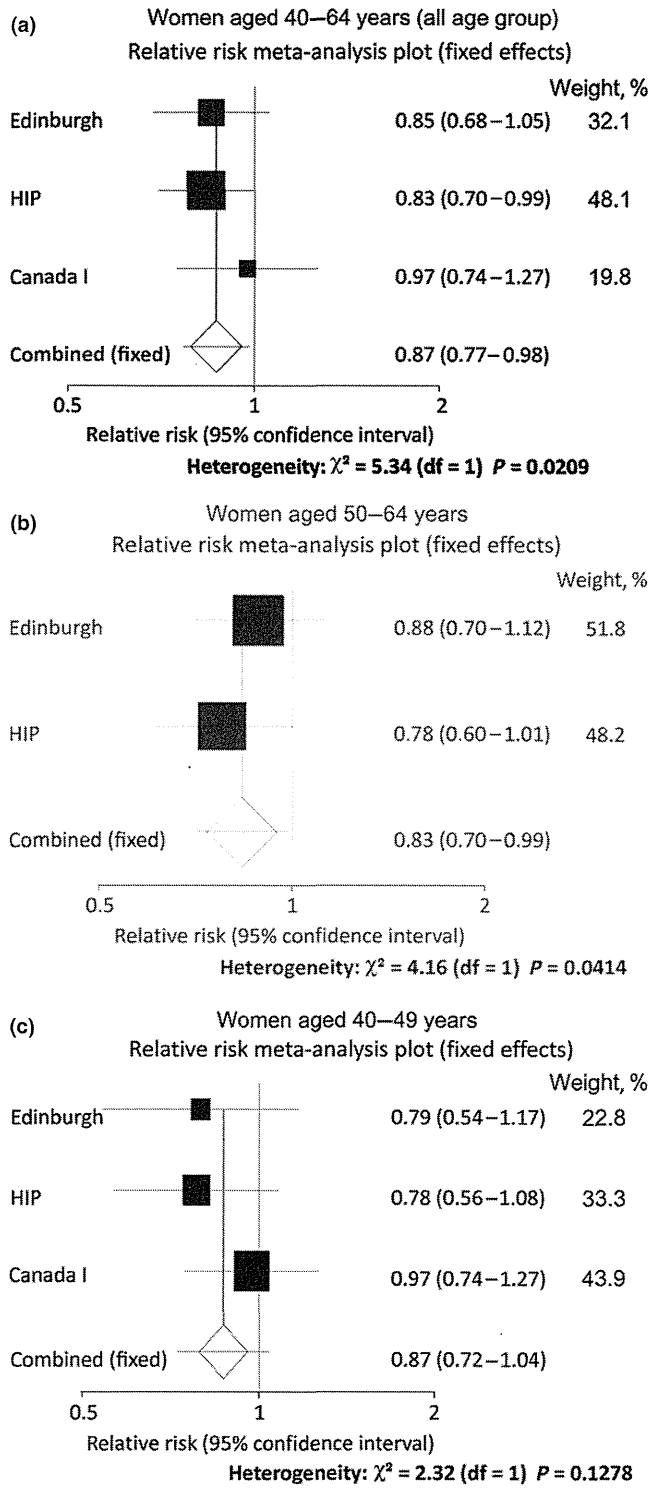

Fig. 2. Meta-analysis of mammographic screening with clinical breast examination. Three randomized controlled trials were identified as eligible: New York HIP study,[28] Edinburgh study,[29] and Canadian study I.[30,31] Women were divided into three target age groups: 40–64 years (all age group) (a); 50–64 years (b); 40–49 years (c).

recommended in developed countries, this method has been commonly used in developing countries.[32] The positive efficacy of clinical breast examination has been suggested by the results of a previous RCT in India.[33] Randomized controlled trials have been performed to evaluate the efficacy of clinical breast examination.[33,34] The sensitivity of clinical breast examination was found to be higher in Japanese studies (50–70%) than in Indian studies.[33,35–37] The results of a Japanese case–control study suggested mortality reduction when symptomatic women were excluded.[38] Despite its advantages, there are serious problems with the continued use of clinical breast examination. Although several studies have reported that training programs could improve the accuracy of clinical breast examination,[39,40] it is difficult to standardize the method because of a lack of an educational system at the national level. Moreover, insufficient human resources can also be a barrier for improving the participation rates of mammographic screening with clinical breast examination in communities. Because of the low accuracy of clinical breast examination, breast ultrasonography has been anticipated as an alternative method that can be combined with mammographic screening. The efficacy of a combination of mammography and ultrasonography in Japan has been evaluated.[41]

There has been significant discussion whether or not to include women aged 40–49 years in the target population of mammographic screening. In 2009, the US Preventive Services Task Force changed its policy for women aged in their 40s and stopped its recommendation of routine screening.[4] The Task Force suggested that women aged in their 40s should have the individual autonomy to choose whether or not to participate in mammographic screening based on shared decision-making with their family physicians. In most European countries, women aged in their 40s have not been included in the target population for breast cancer screening.[6] After the publication of the new guidelines of the US Preventive Services Task Force, the appropriateness of the target age group was carefully examined in previous studies.[5,8,42,43] The results of these studies were similar with regard to women aged in their 40s, that is, not to include them in the target population. However, as the distribution of breast cancer incidence is different in East Asian countries, the same conclusion could not be easily obtained. Although the benefit of mammographic screening is lower in women aged in their 40s, the data for NNI calculation was based on the results of RCTs conducted in Western countries. The proportion of dense breast in women aged in their 40s is higher in Japan than in Western countries[42] and this leads to a lower accuracy of mammographic screening. To resolve the local problem in Japan, a study evaluating mortality reduction from breast cancer among women aged in their 40s is required.

To effectively introduce population-based screening, the balance of benefits and harms of cancer screening must be considered.[6] However, measurement methods for quantitative assessment have not yet been standardized to date. Although NNI is commonly used, the appropriate threshold for the balance of benefits and harms remains unclear. Even if the threshold can be defined, it can be changed considering the local context in terms of disease burden and medical resources. From previous studies, we attempted to evaluate the benefits and harms using the results of meta-analysis of RCTs and available Japanese data. In the Japanese situation, the benefits were always higher in women aged 50 years and over. As there is still no standard established in Japan, the appropriateness of including women aged in their 40s in the NNI cannot be ascertained.

There are additional limitations of this study. First, since most of the RCTs assessed were started before 1990, mammographic equipment use during that time might have been dif-

Table 3. Comparison of benefit and harm between mammographic screening with and without clinical breast examination (CBE)

Screening method	Target age						
	40 years	45 years	50 years	55 years	60 years	65 years	70 years
Mammographic screening without CBE							
Per 1000 women screened							
Number of recalls	77	77	67	67	53	53	53
Per single death prevented							
Number needed to invite	2530	1713	864	777	782	807	833
Number of recalls	195	132	58	52	41	43	44
Mammographic screening with CBE							
Per 1000 women screened							
Number of recalls	99	99	76	76	62	62	62
Per single death prevented							
Number needed to invite	3698	2504	1474	1325	1334	1376	1420
Number of recalls	366	248	112	101	83	85	88

Numbers needed to invite are expressed per 1000 women invited for 13-year follow-up.

ferent from contemporary equipment. At present, even if clinical breast examination is not added, benefits can be obtained, especially with mammography alone. Second, to resolve our research questions, all RCTs using mammography with and without clinical breast examination were included in our analysis. The Edinburgh study is often excluded from the set of evidence because of its inadequate randomization. When this study was excluded, we could not obtain significant results for mammographic screening with clinical breast examination (relative risk = 0.87; 95%CI, 0.75–1.01). Third, Canadian study II was not included in a meta-analysis of mammographic screening without clinical breast examination because the control group underwent clinical breast examination for breast cancer screening. Most guidelines include mammographic screening with clinical breast examination for evaluating the efficacy of mammographic screening.[4,5,8,43,44] The results of our study may show an overestimation of the efficacy of mammographic screening without clinical breast examination. Finally, although the efficacy of mammographic screening without clinical breast examination could be identified for women aged 40–74 years, the efficacy of mammographic screening with clinical breast examination was unclear for women aged 65–74 years because there was no study that included this age group for the target population.

In conclusion, the results of our analysis suggest that mammographic screening without clinical breast examination may afford higher benefits to women aged 50 years and over. Although evidence regarding the effectiveness of mammographic screening without clinical breast examination could be confirmed based on previous RCTs, a Japanese study is needed to resolve local problems, including identification of the appropriate target age group for Japanese women and taking into consideration the balance of benefits and harms.

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Disclosure Statement

The authors have no conflict of interest.

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The Japanese Society of Gastroenterology

SPECIAL ARTICLE

Evidence-based clinical practice guidelines for management of colorectal polyps

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Abstract
Background Recently in Japan, the morbidity of colorectal polyp has been increasing. As a result, a large number of cases of colorectal polyps that are diagnosed and treated using colonoscopy has now increased, and clinical guidelines are needed for endoscopic management and surveillance after treatment.
Methods Three committees [the professional committee for making clinical questions (CQs) and statements by Japanese specialists, the expert panelist committee for rating statements by the modified Delphi method, and the evaluating committee by moderators] were organized. Ten specialists for colorectal polyp management extracted the specific clinical statements from articles published between 1983 and September 2011 obtained from PubMed and a secondary database, and developed the CQs and statements. Basically, statements were made according to the GRADE system. The expert panel individually rated the clinical statements using a modified Delphi approach, in which a clinical statement receiving a median score greater than seven on a nine-point scale from the panel was regarded as valid.
Results The professional committee created 91CQs and statements for the current concept and diagnosis/treatment of various colorectal polyps including epidemiology, screening, pathophysiology, definition and classification, diagnosis, treatment/management, practical treatment, complications and surveillance after treatment, and other colorectal lesions (submucosal tumors, nonneoplastic polyps, polyposis, hereditary tumors, ulcerative colitis-associated tumor/carcinoma).
Conclusions After evaluation by the moderators, evidence-based clinical guidelines for management of colorectal polyps have been proposed for 2014.

Keywords Colorectal polyp · Colorectal tumor · Polyposis · GRADE system

Introduction

In Japan, following the westernization of eating habits and with aging of the population, the morbidity of colorectal carcinoma and associated mortality are both increasing. Indeed, it has been said that the 21st century is the era of the large intestine. As the number of cases of colorectal polyps that are diagnosed and treated via colonoscopy has now increased, clinical guidelines are needed for endoscopic management and surveillance after treatment. In April 2012, the National Health Insurance system began offering coverage for expenses incurred for colorectal endoscopic submucosal dissection (ESD). Accordingly, appropriate selection between ESD and endoscopic

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The members of the Working Committee are listed in the Appendix in the text.

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mucosal resection (EMR) has become more important. In this regard, the Japanese Society of Gastroenterology (JSGE) has established "evidence-based clinical guidelines for management of colorectal polyps" (hereafter referred to as "the Guidelines"). Although the title of the Guidelines mentions colorectal polyps, they include all types of localized colorectal lesions, including superficial neoplastic lesions, early carcinoma, and polyposis.

The Guidelines Creation Committee and Evaluation Committee were established prior to drafting the Guidelines. The Japanese Gastroenterological Association, Japanese Society of Gastrointestinal Cancer Screening, the Japan Gastroenterological Endoscopy Society (JGES), the Japan Society of Coloproctology (JSCP), and the Japanese Society for Cancer of the Colon and Rectum (JSCCR), which are cooperative societies, recommended members to be assigned to these two committees.

In the creation of the Guidelines, the Guidelines Creation Committee drafted clinical questions (CQs) that covered: (1) epidemiology; (2) screening; (3) pathophysiology, definition, and classification; (4) diagnosis; (5) treatment and management; (6) practical treatment; (7) complication and surveillance after treatment; and (8) other colorectal lesions (submucosal tumors, nonneoplastic polyps, polyposis, hereditary tumors, ulcerative colitis-associated tumor/cancer). The Evaluation Committee evaluated the drafts of the CQs, and 91 CQs were established. For each CQ, a document retrieval style was created, and systematic document retrieval was performed by searching PubMed and Igaku Chuo Zassi for articles published between January 1983 and September 2011. For insufficient or unobtainable documents, manual searching was also performed. Subsequently, a structured abstract was created, and both a statement and an explanation were written. The Guidelines Creation Committee determined the grades of recommendations and the levels of evidence after deliberation using the Delphi method. As mentioned in a previous publication [1], the Guidelines were created in accordance with the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system. This draft was evaluated and amended by the Evaluation Committee, which was then presented to members of the JSGE. After obtaining public comments, these comments were discussed, and a final version of the Guidelines was created.

The contents on tumor diagnosis and endoscopic treatment described in the Guidelines partially overlap with those of the previously published 2014 JSCCR Guidelines for the Treatment of Colorectal Cancer [2] and the Colorectal ESD/EMR Guidelines (JGES) [3]. In addition, the committees for these three guidelines closely cooperated with each other to ensure their consistency. Concerning the contents of the Guidelines, this paper mainly introduces CQs for the treatment of colorectal polyps.

Clinical questions (CQ) and statements

CQ. What are the indications for endoscopic resection with respect to the size of adenomas?

- Endoscopic resection should be used for lesions ≥6 mm in size (Recommendation 2 [100 %], level of evidence C). However, endoscopic resection should also be used for diminutive lesions ≤5 mm, flat and depressed lesions, as well as for those indistinguishable from carcinoma (Recommendation 2 [100 %], level of evidence D).

Comment: It is strongly recommended that endoscopic resection be used for lesions ≥6 mm in size because the incidence of carcinoma is higher in lesions ≥6 mm than in those ≤5 mm, and because it is often difficult to distinguish between benign adenomas and carcinomas by colonoscopy alone [4, 5].

According to a study in the UK, if the relative risk for carcinoma in lesions ≤5 mm is considered 1, it increases to 7.2, 12.7, and 14.6 in lesions sized 6–10 mm, 11–20 mm, and >20 mm, respectively. Therefore, all colonic lesions ≥6 mm should be either resected or ablated [4]. From the results of meta-analyses, polypectomy [4] and EMR [6]/ESD [7] can be considered the preferred less invasive treatments for colorectal neoplasia [8, 9]. However, for flat and depressed lesions, endoscopic resection is recommended, since the incidence of carcinoma is even higher in lesions that are ≤5 mm in size than in polypoid lesions [6, 10].

CQ. How should diminutive adenomas that are ≤5 mm in size be managed?

- Diminutive polypoid lesions should be followed up (Recommendation 2 [100 %], level of evidence C). However, endoscopic resection should be performed for diminutive flat and depressed lesions that are difficult to distinguish from adenomas or carcinomas (Recommendation 2 [100 %], level of evidence D).

Comment: Hyperplastic diminutive lesions ≤5 mm in size are acceptable for being followed up by colonoscopy. In diminutive polypoid adenomas ≤5 mm, at least in principle, follow-up is acceptable in the absence of colonoscopic findings suggestive of carcinoma. Flat and depressed lesions suspected of being adenoma or carcinoma on colonoscopy are preferably treated by endoscopic resection. Colonoscopic findings suspicious for carcinoma include the following: (1) expansive appearance (protrusion and overextension of the lesion and/or surrounding normal mucosa such as a submucosal tumor); (2) depressed surface; (3) rough appearance (rough surface without shine); (4) normal mucosa of the border of the tumor in

sessile lesions; and (5) type V pit pattern (irregular or disappearance of surface structure). To confirm these findings, chromoendoscopy or magnifying colonoscopy is recommended [11, 12]. Diminutive lesions should be followed up with annual colonoscopy for 3 years [13, 14].

A cohort study on diminutive colorectal lesions reported that there is little change in either the size or shape of lesions after 2–3 years of follow-up [13]. The incidence of carcinoma in diminutive colorectal lesions in Western countries is reported to range from 0.03 to 0.05 %. According to a large-scale cohort study, the overall incidence of polypectomy-related complications is 0.7 % with a perforation rate of 0.1 % (one per 1,000 resections). In addition, to decrease unnecessary risks for healthy individuals and lower overall costs, endoscopic resection should not be performed for all diminutive colorectal lesions ≤5 mm [15, 16].

After resection of colorectal neoplasia, yearly follow-up by colonoscopy is recommended until all colorectal polyps including diminutive lesions have been completely excised, and every 3 years thereafter [14, 17].

CQ. How should hyperplastic polyps be managed?

- Follow-up is recommended for hyperplastic polyps ≤5 mm detected in the recto-sigmoid region (Recommendation 2 [100 %], level of evidence D). Endoscopic resection should be performed for lesions ≥10 mm detected in the right side of the colon, as they are difficult to discriminate from sessile serrated adenoma/polyps (SSA/P) (Recommendation 2 [100 %], level of evidence D).

Comment: Typical hyperplastic polyps presenting as whitish flat lesions ≤5 mm in the recto-sigmoid region should be followed up, as there have been no reports on the association of these lesions with adenoma [18, 19]. Colonoscopy every 10 years is recommended in the case of hyperplastic polyps according to the guidelines of the AGA/ASGE. Endoscopic resection should be used for lesions ≥10 mm in size in the right side of the colon, as they are difficult to distinguish from SSA/P; the incidence of carcinoma in such lesions has been reported to be 9.4 % [20].

According to the results of 1,800 cases in two large studies on chemoprevention, the risk of hyperplastic polyps is significantly higher (OR 3.67; $p < 0.001$) in patients with hyperplastic polyps detected at initial examination. Moreover, the risk of relapse of adenomatous polyps is also significantly higher (OR 2.08; $p < 0.01$) in patients with adenomatous polyps detected at initial examination. On the other hand, there is no correlation between the risk of adenoma and detection of hyperplastic polyps at initial examination or between adenomatous polyps and the presence of hyperplastic polyps [18, 19]. It has been hypothesized that adenomatous and hyperplastic polys may have different etiology, since the presence of the former has no correlation with the latter, and vice versa [18, 19].

However, one report has suggested that hyperplastic polyps in the recto-sigmoid region may indicate malignant lesions in the proximal colon, since *BRAF* mutations have been detected in hyperplastic polyps, although additional investigations are needed to clarify potential correlations between hyperplastic polyps and SSA/P [18, 19].

CQ. How should serrated lesions of the colorectum be treated?

- Serrated lesions of the colorectum include sessile serrated adenoma/polyp (SSA/P), traditional serrated adenoma (TSA), and hyperplastic polyp (HP). The former two lesions have potential to develop to adenocarcinoma and thus are recommended to treat (Recommendation 2 [100 %], level of evidence D).

Comment: Serrated lesions of the colorectum include SSA/P, TSA, and HP. SSA/P and TSA may undergo malignant transformation to adenocarcinoma and should thus be treated. SSA/P is associated with *BRAF* mutations and the CpG island methylator phenotype (CIMP), and is considered a precursor lesion of colorectal carcinoma with microsatellite instability [21]. Recent studies have reported that the rate of progression to carcinoma in SSA/P ranges from 1.5 to 20 % [22]. Aggressive resection should be performed for SSA/P [23].

TSA is a protruding lesion with distinct redness that is commonly found in the left side of the colon and rectum. Histologically, TSA is considered to potentially progress to carcinoma, similar to SSA/P. Treatment is therefore indicated for TSA, and resection is indicated for TSA ≥5 mm in diameter, similar to common adenomas. As for SSA/P, most studies recommend that lesions ≥10 mm in diameter should be resected [24–26]. HP may be a precursor lesion of SSA/P and/or TSA. Treatment is not indicated for HP ≤5 mm in diameter.

CQ. What therapy is indicated for laterally spreading tumors (LST)?

- The therapeutic choice between piecemeal EMR and ESD for a large LST should be based on the LST subtype, and use of magnifying endoscopy and endoscopic ultrasonography as appropriate (Recommendation 2 [100 %], level of evidence C).

Comment: LSTs are classified into two types according to morphology: granular type (LST-G) and non-granular type (LST-NG) [27]. Each type has two subtypes. The former consists of a "homogenous type" and a "nodular mixed type", while the latter consists of a "flat elevated type" and

a "pseudo-depressed type". Most LST-Gs are considered adenomatous lesions. Among homogenous-type LST-Gs, the incidence of carcinoma or submucosal invasion is extremely low [28, 29]. Large nodule in a nodular mixed-type LST-G, where submucosal invasion tends to be present [30], should be resected en bloc [31]. An adenomatous LST-G homogenous type can be resected by piecemeal EMR [32]. A flat elevated-type LST-NG should be treated according to preoperative diagnosis. For pseudo-depressed-type LST-NGs, en bloc resection should be performed, since these tumors have a high probability of multifocal submucosal invasion independent of their size or pit pattern [30, 31]. In summary, the indications for ESD or piecemeal EMR are based on the LST subtype; magnifying endoscopy and endoscopic ultrasonography are used as needed.

CQ. What are the indications for endoscopic resection of early colorectal carcinoma?

- An early colorectal carcinoma (Tis/T1) should be treated endoscopically when the possibility of lymph node metastasis is extremely low and en bloc resection is possible (Recommendation none, level of evidence level C).

Comment: There are no reports of lymph node metastasis in intramucosal (Tis) carcinomas, while lymph node metastasis occurs in approximately 10 % of submucosal invasive (T1) carcinomas [33, 34]. Therefore, endoscopic resection is recommended in a Tis or Tl carcinoma that has a low probability of lymph node metastasis. Endoscopic resection is both a therapeutic and important diagnostic method that can be used for total excisional biopsy. Complete resection with a negative vertical margin is indispensable for cure after endoscopic resection of a T1 carcinoma. Endoscopic resection of T1 carcinomas is associated with a risk of positive vertical margins. It is thus necessary to completely resect the carcinoma and ensure that horizontal and vertical margins are negative, enabling both precise pathological diagnosis and curative potential [2].

CQ. What pathological findings do indicate additional surgery after endoscopic resection for early colorectal carcinoma?

- T1 carcinoma with a tumor-positive vertical margin is an absolute indication. T1 carcinoma with an unfavorable histologic grade or submucosal invasion of $\geq$1,000 μm, or vascular invasion or grade 2/3 tumor budding should be considered for additional surgery with lymph node dissection (Recommendation none, level of evidence C).

Comment: Lymph node metastasis is found in 6.8–17.8 % of T1 carcinomas [2, 35, 36]. In principle, T1 carcinoma should be treated by surgery with lymph node dissection. The risk factors for lymph node metastasis in T1 carcinoma include depth of submucosal invasion [2, 35, 37–42], histological grade [2, 35, 37, 39–42], budding grade [2, 35, 36, 43], and vascular invasion [2, 35–44]. According to the 2014 guidelines by the JSCCR (Japanese Society for Cancer of the Colon and Rectum) for the treatment of colorectal carcinoma, among the carcinomas treated by endoscopic resection, T1 carcinomas with a tumor-negative vertical margin, favorable histologic grade with a submucosal invasion depth of <1,000 μm, and absence of vascular invasion with tumor budding grade 1 (low grade) could be followed up, while T1 carcinomas that do not meet these criteria should be considered for additional surgery with lymph node dissection. It may possible to reduce the number of patients undergoing unnecessary additional surgical resection considering the above risk factors [2, 37–39, 45, 46]. Even if the risk for lymph node metastasis after endoscopic treatment cannot be considered zero, a comprehensive assessment of the pathologic findings after endoscopic resection, patient age, physical activity levels, comorbidities, and any potentially undesirable consequences of the resection such as urinary and excretory disorders or the need for colostomy is needed.

CQ. In which types of colorectal tumors is it acceptable to perform piecemeal EMR?

- Definite adenoma or Tis carcinoma based on preoperative diagnosis are acceptable for piecemeal EMR. However, rates of local recurrence with piecemeal resection are high, and thus caution is advised (Recommendation 2 [100 %], level of evidence C).

Comment: In principle, en bloc resection should be used for suspicious or definite carcinoma, since the specimen obtained by complete en bloc resection should be pathologically examined in detail. On the basis of precise preoperative diagnosis with magnifying endoscopy, adenomatous lesions or focal carcinoma in adenomas $\geq$2 cm in diameter, for which en bloc snare EMR is not indicated, can be completely resected using deliberate piecemeal EMR to avoid segmentation of the carcinomatous area without compromising pathological diagnosis [2]. Although the local recurrence rate associated with piecemeal resection is high compared with that after en bloc resection [31, 32, 47–52], most local recurrent lesions are adenomas. Cure is possible with additional endoscopic treatment for local recurrent intramucosal lesions [47, 49, 52, 53]. In contrast, ESD allows complete en bloc resection regardless of lesion size. However, colorectal ESD is