Downloaded from http://gut.bmj.com/ on March 24, 2015 - Published by group.bmj.com

conventional colonoscopy or FIT in a 10-year simulation model assessing asymptomatic average-risk population 50–74 years of age, CTC is not the most cost-effective method for CRC screening.[54] CTC with non-reporting of diminutive lesions was found to be the most cost-effective and safest screening option evaluated according to a study conducted by radiology experts.[55] However, in Asia, polyps measuring 6–9 mm and <5 mm may still have a substantial risk of advanced neoplasia and invasive cancer.[56] Non-reporting policy for small polyps may not be entirely safe.

Statement 10: Capsule endoscopy: A role for capsule endoscopy in CRC screening is not defined. It may be used in cases when total colonoscopy is not possible.

Level of agreement: A=63.9%, B=33.3%, C=2.8%, D=0%, E=0%.

Quality of evidence: II-2.

Classification of recommendation: B.

Capsule endoscopy has been tested in comparison to conventional colonoscopy for the detection of colorectal polyps and cancer. In a prospective multicentre study from Europe, the first-generation capsule endoscopy was found to be able to detect polyps 6 mm or larger with a sensitivity of 64% and specificity 84%. Cancer detection was achieved in 14 out of 19 cases (74%).[57] This result has room for improvement.

In the second-generation capsule endoscopy for colon (PillCam Colon 2), frame speed has been increased from a fixed speed of 4 pictures per second to a variable 4–35 pictures per second depending on the capsule movement. The angle of view has also been widened from 156 to 172° on both ends. These improvements should be able to improve performance of capsule endoscopy. Two prospective controlled studies have been conducted from Israel and Europe to compare the new-generation capsule endoscopy with conventional colonoscopy. The sensitivity of detecting polyps ≥6 mm in size was reported as 84–89% and with a corresponding specificity of 76–92%.[58 59]

The most recent study enrolled 884 patients from 16 centres in the USA and Israel.[60] The sensitivity and specificity for detecting adenomatous polyps ≥6 mm in size were 88% and 82%, and for detecting adenomatous polyp ≥10 mm in size were 92% and 95%, respectively. All patients with CRC were detected by capsule endoscopy in this study. The report also indicated that capsule endoscopy is safe and well tolerated by patients and hence might improve the acceptance and adherence in a screening programme.[60]

In the recent European Society for Gastrointestinal Endoscopy Guideline for Colon Capsule Endoscopy, international experts have recommended capsule endoscopy as a feasible and safe tool for visualisation of the colonic mucosa in patients with incomplete colonoscopy.[61] They further commented that patients at high risk of CRC should be referred for colonoscopy. However, in patients for whom colonoscopy is inappropriate, failed to be completed or not possible, the use of capsule endoscopy could be discussed with the patient. The Asia Pacific Working Group accepts this recommendation and has included this in the current consensus.

WHO SHOULD BE CONSIDERED FOR EARLIER SCREENING?

Statement 11: First-degree relatives of patients with sporadic CRC diagnosed at age <50 are at an increased risk of colorectal neoplasm and early screening is warranted.

Level of agreement: A=63.9%, B=33.3%, C=2.8%, D=0%, E=0%.

Quality of evidence: II-2.

Classification of recommendation: B.

Family members of inherited diseases such as familial adenomatous polyposis, Peutz–Jeghers syndrome and Lynch syndrome need to receive timely genetic and screening for CRC. In this consensus, we focused on non-inherited subjects or sporadic CRC, which accounts for 70% of familial CRC.[62]

Familial clustering of CRC is a well-known phenomenon, and it has been estimated that the first-degree relatives (FDR) of CRC patients have a threefold increased risk of dying from CRC.[63] The risk of CRC appears to increase with the number of CRC-affected FDR.[64] The risk is inversely associated with the age at which CRC was diagnosed in affected family members. Several meta-analyses based on case–control and cohort studies have indicated that the risk ranges from 2–3-fold to 3–4-fold.[65–67]

All societies (ACS/USMSTF/ACR and BSG) recommended earlier screening of FDR of patients with an adenoma before the age of 60. The guidelines recommend that screening should start at 40 years of age.[11] However, the evidence in support of this statement was based on retrospective studies. Prospective data assessing the risks of CRC in FDR of patients with adenoma are lacking. It has been suggested that screening for FDR of patients with adenoma is too aggressive.[68]

Recent studies have shown that among FDR of index cases with CRC the frequency of adenoma detection is also elevated. A study from Taiwan reported that among FDR of patients with CRC the risk of adenoma detected by colonoscopy was 2.5-fold and the risk of high risk adenoma was 4.5-fold compared with control subjects who had no family history of CRC.[69] A study from Hong Kong compared the risk of advanced neoplasms among asymptomatic FDR of patients with CRC to those with a negative family history of CRC.[16] The risk of detecting adenoma was 2.19-fold, and the risk of detecting advanced neoplasms was 3.07-fold increased in the first group. The increased risk is more remarkable if the index case had been diagnosed with CRC before the age of 50 years. This study indicates that performing CRC screening among FDR of CRC patients allows earlier detection of cancer and may provide an effective way to prevent cancer development through colonoscopic polypectomy. Therefore, early screening for FDR of patients with CRC is warranted.

Statement 12: A stratified screening approach based on the risk for CRC is recommended.

Level of agreement: A=72.2%, B=25%, C=2.8%, D=0%, E=0%.

Quality of evidence: II-3.

Classification of recommendation: B.

While colonoscopy may provide the best single examination of the colon and opportunity of polypectomy, it carries a heavy burden on healthcare systems that may not be feasible in some resource-limited countries. On the other hand, the cost of colonoscopy and its invasive nature is prohibitive for those who are unwilling to pay for the examination and for some elderly subjects.[70 71] One way to reduce the cost and the workload of CRC screening by colonoscopy is to adopt a stratified approach. A study from Taiwan proposed to use age as a triage to direct younger subjects, for example, below the age of 60 years to receive FS.[72] Screening subjects with an adenoma in the distal colon are offered a full colonoscopy. On the other hand, colonoscopy is offered to all above the age of 60 years as they have a higher frequency of having adenoma.

The Asia Pacific Working Group on CRC screening has developed a risk-stratifying system using four risk factors (age, gender, family history and smoking habit). This simple scoring

Downloaded from http://gut.bmj.com/ on March 24, 2015 - Published by group.bmj.com

system can be used to identify moderate-to-high-risk individuals requiring colonoscopy.[20] In contrast, an FIT is sufficient for the average risk individuals followed by colonoscopy in case of a positive result. This scoring system has recently been validated in 15-country multicentre Asian study that recruited asymptomatic subjects.[21]

The consensus panel considered risk stratification based on a few simple demographic parameters as a useful approach for CRC screening with the benefits of reduced burden and increased affordability for the healthcare system. The scoring system can be modified for regional usage and the triage system can be adapted to the local resources and needs. However, some kind of risk stratification would increase adherence to the CRC screening strategy through improved motivation.

HOW TO MINIMISE MISSED LESIONS OR INTERVAL CANCERS?

Statement 13: Surveillance interval for colonoscopy should be tailored to risk for colorectal neoplasia.

Level of agreement: A=86.1%, B=13.9%, C=0%, D=0%, E=0%.

Quality of evidence: II-1.

Classification of recommendation: A.

There are two main questions regarding the appropriate time for surveillance colonoscopy: (i) When should colonoscopy be repeated after a negative examination? (ii) When should colonoscopy be repeated after an adenoma is removed?

The USMSTF guideline on CRC screening recommends that the interval of colonoscopy surveillance should depend on the findings at the baseline colonoscopy. Those with a low-risk adenoma (defined as 1–2 tubular adenoma <10 mm) can have a repeat colonoscopy in 10 years. Those with a high-risk adenoma (defined as adenoma with villous histology, high-grade dysplasia, >10 mm, or three or more adenomas) should have a shorter surveillance interval in 3 years.[73 74] The European guidelines stratified risk into three levels: low risk (1–2 adenoma <10 mm), intermediate risk (3–4 small adenoma or one >10 mm) and high risk (>5 small adenomas or >3 with at least one >10 mm). They recommend that the high-risk group undergo surveillance at 1 year, the intermediate-risk group at 3-yearly intervals until two consecutive examinations are negative and the low-risk group requires no surveillance colonoscopy or 5-yearly colonoscopy until one negative examination after which surveillance can be ceased.[5]

Cohort studies have shown that after a negative colonoscopy the risk of identifying an advanced neoplasm ranges from 1.3 to 2.4%, practically the same as the baseline risk in the general population.[75–78] Three studies have shown that 10 years after CRC screening, a negative colonoscopy was associated with a subsequent reduced risk of developing CRC (adjusted OR 0.26).[79–81] Based on this evidence, the latest AGA recommendation is that 10 years would be the appropriate interval for repeating colonoscopy after a negative examination in subjects with no family history of CRC.[74] For those who have family history of CRC before the age of 60 years, it was recommended that a repeated examination should be conducted in 5 years.

More recently, the USMSTF published their revised guidelines on colonoscopic surveillance after screening and polypectomy with additional criteria.[74] Basically, the surveillance interval depends on (i) findings of polyps (hyperplastic or adenoma), (ii) number and size of adenomas, (iii) the presence of villous architecture and high-grade dysplasia of the adenoma and (iv) the presence of serrated lesions or serrated polyposis syndrome (>20 serrated polyps of any size throughout the colon). The interval of screening or surveillance is recommended from 1 to 10 years depending on the risk stratification (table 4).

A multicentre retrospective cohort study from Japan showed that patients with any adenoma ≥6 mm or intramucosal cancer at the initial colonoscopy have a high risk of advanced neoplasia in subsequent colonoscopy.[82] The risk is more significant in the right colon, a feature probably related to the higher frequency of non-polypoid lesions found in this location. In view of this concern, the Japan Polyp Study (JPS), which is a multicentre RCT conducted in 11 centres since 2003 is currently evaluating the risk of colorectal neoplasia one year after a 'clean' colonoscopy. Final follow-up results of this important study are still pending.[83]

The Asia Pacific Consensus group recommended that surveillance interval should be tailored to the risk level. However, since there is in general a lack of prospective data, precise guidelines on interval of surveillance cannot be given.

Statement 14: Right-sided lesions and sessile serrated polyps can be difficult to detect and contribute to interval cancers.

Level of agreement: A=77.8%, B=19.4%, C=2.8%, D=0%, E=0%.

Quality of evidence: II-2.

Classification of recommendation: A.

Sessile serrated polyps were once thought to have little clinical implications, but ample evidence now shows that they represent an alternate pathway of colorectal carcinogenesis. The serrated pathway associated with these lesions involves an epigenetic aberrant mechanism with abnormal hypermethylation of CpG islands located in the promoter regions of tumour suppressor genes. BRAF mutation is often involved. There are three distinct subtypes of serrated neoplasia: hyperplastic polyp (70%), sessile serrated adenoma (25%) and traditional serrated adenoma (5%). The last two forms are considered to be precursors of CRC. These lesions are usually flat or sessile, large and occasionally covered by a mucous cap. They are commonly

Table 4 Recommendations for surveillance and screening intervals after baseline colonoscopy: adapted from US Multi-Society Task Force on Colorectal Cancer Guidelines for Colonoscopy Surveillance after screening and polypectomy[66]

Baseline colonoscopy: most advanced finding(s)	Recommended surveillance interval (years)
No polyps	10
Small (<10 mm) hyperplastic polyps in rectum and sigmoid	10
1–2 small (<10 mm) tubular adenomas	5–10
3–10 tubular adenomas	3
>10 adenomas	<3
One or more tubular adenomas ≥10 mm	3
One or more villous adenomas	3
Adenoma with high-grade dysplasia	3
Serrated lesions	
Sessile serrated polyp(s) <10 mm with no dysplasia	5
Sessile serrated polyp(s) ≥10 mm OR	3
Sessile serrated polyp with dysplasia OR	
Traditional serrated adenoma	
Serrated polyposis syndrome	1

Serrated polyposis syndrome: Based on the WHO definition of serrated polyposis syndrome, with one of the following criteria: (1) at least five serrated polyps proximal to sigmoid, with two or more >10 mm; (2) any serrated polyps proximal to sigmoid with family history of serrated polyposis syndrome; and (3) >20 serrated polyps of any size throughout the colon.

Downloaded from http://gut.bmj.com/ on March 24, 2015 - Published by group.bmj.com

found in the proximal colon and, because of their flat appearance, could be easily missed.

There is accumulating evidence that a sizeable proportion of interval cancers is related to these sessile serrated polyps. There are more interval cancers found in the proximal colon (6–14%) than in the distal colon (2–7%).[84–87] The molecular characteristics of interval cancers are also significantly different from non-interval cancer with higher prevalence of microsatellite instability (30% vs 10%), less KRAS mutation (13% vs 29%), higher CpG island methylator phonotype (57% vs 33%) and BRAF mutation (28% vs 19%).[88–90] These evidences point to the fact that sessile serrated lesions in the proximal colon are frequently missed and present subsequently as interval cancers. Therefore, the Asia Pacific Consensus group felt that there is a need to emphasise the need for meticulous examination of the proximal colon.

Statement 15: Colonoscopy: Good quality colonoscopy is key to success of a screening programme and quality of colonoscopy should be audited.

Level of agreement: A=86.1%, B=11.1%, C=0%, D=2.8%, E=0%.

Quality of evidence: II-2.

Classification of recommendation: A.

The effectiveness of screening and diagnostic colonoscopy in reducing CRC mortality depends on adequate visualisation of the entire colon, diligence in examining the mucosa, successful removal of premalignant lesions and a proper follow-up. Quality indicators include appropriate indication, bowel preparation quality, colonoscope withdrawal time from the caecum, adenoma detection rate, appropriate surveillance interval and adverse or unplanned events after colonoscopy. The importance of quality colonoscopy cannot be overemphasised for the success of a screening programme. Quality of colonoscopy can be assessed by the rates of successful caecal intubation, avoidance of missed lesions, completeness of lesion removal and prevention of adverse events (table 5).

Table 5 Quality indicators for colonoscopy screening and surveillance

Colonoscopy quality indicator by type	Examples
Documentation	Patient demographics Preprocedure assessment of risk Appropriate indication of procedure Documentation of prior exam and interval Technical description of the procedure Documentation of quality of bowel preparation Description of colonoscopic findings and management Recording of unplanned events and interventions Follow-up plan
Performance	Caecal intubation with documentation Adenoma or polyp detection rate Withdrawal time at least 6 min Immediate unplanned events or interventions
Follow-up/communication	Appropriate documentation of pathology Recommended follow-up/surveillance interval consistent with evidence-based guidelines or rationale for deviation from guideline Communication to primary provider and patient
Key outcomes	Interval colorectal cancer Adverse events

Adapted and modified from Lieberman.[74 124]

The adenoma detection rate of a colonoscopist is identified as one of the most reliable quality indicators.[91–93] A large-scale study from Poland showed that the endoscopist's rate of detection of adenomas is significantly associated with the risk of interval CRC.[91] Besides the skills of the endoscopists, bowel preparation (including the use of split preparation)[94 95] and endoscope withdrawal time (more than 8 min)[96–98] have been reported as important modifiable factors that influence the adenoma detection rate.[99]

There are initiatives from various countries to audit and monitor colonoscopy quality and auditing programmes.[93 100–102] The Asia Pacific Consensus group strongly believes that an audit system should be introduced in each country or region on the quality of colonoscopy.

Statement 16: Colonoscopy: Ancillary methods with the exception of chromoendoscopy have not proven to be superior to high-definition white light endoscopy in identifying adenoma.

Level of agreement: A=63.9%, B=36.1%, C=0%, D=0%, E=0%.

Quality of evidence: I.

Classification of recommendation: A.

High-definition white light colonoscopy with high-definition video processor and high-definition monitor are best for identification of adenomas in the colon. Pooled data from five studies showed the superiority of high-definition white light colonoscopy in detecting all polyp types and adenomas compared with conventional white light colonoscopy.[103] A more recent prospective study also showed that high-definition white light colonoscopy has a higher adenoma detection rate[104] (Table 6).

Chromoendoscopy, using a indigo carmine (0.1–0.4%), crystal violet (0.5%) or methylene blue (0.1%) on the surface of the mucosa to highlight the pits and pools dyes in the mucosal crevices, is a well-established method in colonoscopy. Compared to high-definition white light colonoscopy, high-definition chromoendoscopy in average-risk CRC screening has been shown to marginally increase in the detection of flat lesions and small adenoma detection.[105 106] By pooling results of five prospective randomised studies, the Cochrane Review confirmed that chromoendoscopy detects at least one neoplastic lesion per colonoscopy more than conventional colonoscopy, but the withdrawal time is significantly longer than conventional colonoscopy.[107]

Narrow band imaging (NBI) uses specific filtered wavelengths in the bands of blue (400–430 nm) and green (530–550 nm)

Table 6 Endoscopic imaging modalities and efficacy in CRC screening

Technology	Effective in improving adenoma detection rate	Hassle free	Available
High-definition white light	Probably yes	Yes	Yes
Chromoendoscopy	Yes	No	Yes
NBI	No	Yes	Yes
FICE	No	Yes	Yes
I-scan	Mixed (limited data)	Yes	Yes
AFI	Mixed	Yes	No
Cap-assisted colonoscopy	Mixed	Yes	Yes
Third eye retroscope	Yes (limited data)	No	Yes

AFI, autofluorescence; CRC, Consensus on Colorectal Cancer; FICE, Fujinon Intelligent Colour Enhancement system; NBI, narrow band imaging.

Downloaded from http://gut.bmj.com/ on March 24, 2015 - Published by group.bmj.com

light to illuminate the mucosa leading to deeper penetration of light and enhancement of superficial mucosa and vascular pattern. A recent study showed that NBI can better differentiate neoplastic from non-neoplastic polyps.[108] Yet six clinical studies and their pooled data failed to demonstrate that using NBI endoscope will increase the detection rates for adenoma.[109] This was confirmed by a Cochrane Database review based on 11 studies comparing white light colonoscopy and NBI.[110] Similarly, the Fujinon Intelligent Color Enhancement system (FICE) fails to provide any advantages.[111–113] Autofluorescence (AFI) technology also failed to demonstrate significantly better results in the detection of flat lesions and adenoma.[114 115] So far, none of the new imaging modalities have proven advantage over white light colonoscopy, but this does not preclude future advancement in imaging technology may break the ground.

Cap-assisted colonoscopy helps to flatten haustral folds and keeping the mucosa at an appropriate distance from the lens. This technique does not require any expensive equipment or specific training. It may improve visualisation of the proximal aspects of folds and flexures of the colon. In 16 RCTs including close to 9000 subjects, cap-assisted colonoscopy showed marginal benefit over conventional colonoscopy with an 8% increase in polyp detection, 0.64 min shorter time for caecal intubation and a shortened procedure time.[116]

The third-eye retroscope is an auxiliary device that passes through the working channel of the colonoscope and permits a wider angle of vision with a retroflexed visualisation of the proximally facing mucosal folds commonly missed during conventional colonoscopy. The Third Eye Retroscope Randomised Clinical Evaluation (TERRACE) was a randomised controlled, multicentre trial that suggested that the third-eye retroscope increases adenoma detection compared with the conventional colonoscope.[117 118] There are so far insufficient data to support endorsing their usage in routine screening for colorectal neoplasia.

Statement 17: All components of a CRC screening programme should be audited and quality controlled.

Level of agreement: A=88.9%, B=11.1%, C=8.3%, D=0%, E=0%.

Quality of evidence: III.

Classification of recommendation: C.

CRC screening is not a single diagnostic test but a sophisticated programme that involves logistics, resource availability, clinical skills, education and population acceptance and adherence. The Asia Pacific Consensus group strongly believe that all components of a CRC screening programme need to be audited and the quality of individual components be subjected to quality control on a regular basis.

The UK National Health Service Bowel Cancer Screening Program introduced a set of monitoring parameters including selection of screening subjects, call-and-recall mechanism, logging receipt of test kits and test results, booking of clinic appointments, recording of colonoscopy and histopathology results, and reporting programme activities in their quality assurance programme (http://www.cancerscreening.nhs.uk/bowel). The ACS/USMSTF/ACR guideline emphasises on quality assurance of screening modalities, training requirement, optimal techniques to complete the examination, screening intervals and appropriate recommendations on follow-up.[11] The European guidelines for quality assurance in CRC screening issued the most comprehensive sets of criteria including quality assurance of endoscopy, professional requirement and training, quality assurance of pathology, management of lesions detected, colonoscopic surveillance following adenoma removal and communications with subjects.[9]

As Asia represents a heterogeneous group of countries and regions with different healthcare systems, resource commitment and population health behaviour, the group did not attempt to propose a single quality assurance programme for the whole region. However, an audit system to monitor the performance and effectiveness of CRC screening programmes in this region is strongly recommended and the audit should be conducted on a regular basis.

OTHER ISSUES

Statement 18: Trained nurse endoscopists are able to perform flexible sigmoidoscopy and colonoscopy effectively.

Level of agreement: No consensus reached.

Quality of evidence: II-2.

Classification of recommendation: Not applicable.

Because of a shortage of colonoscopy workforce for CRC screening, there is suggestion of using trained nurse endoscopists to perform colonoscopy or FS. Studies of nurse endoscopists have been reported from the UK, US and some European countries, but comparative data from large-scale prospective randomised trials are lacking. In a landmark study by Maule *et al*,[119] nurse endoscopists were reported to be safe and accurate in performing FS in CRC screening. A recent study also demonstrated that nurse endoscopists performed colonoscopies with high patient satisfaction.[120] The BSG Working Group has endorsed nurse endoscopists in performing FS.[121] On the other hand, the ASGE guideline did not recommend nurses to perform colonoscopy.[122] In a small-scale non-randomised study in USA, the nurse-endoscopist outperformed medical endoscopist by detecting 2.5-fold more adenoma.[123]

In Hong Kong, a prospective, randomised controlled single-blinded study enrolled 731 patients to receive colonoscopy by either nurse-endoscopist or physician-endoscopists (Hui *et al*, submitted). The nurse-endoscopist group had a higher adenoma detection rate than physician-endoscopist group (44% vs 33%) but required a significantly longer withdrawal time. Caecal intubation rate and complication rate were similar in both groups. In the Asia Pacific Consensus group, a vigorous debate was conducted on whether nurses should be trained to perform colonoscopy and polypectomy under strict guidelines and physician supervision. Due to a divergence of opinions from several countries identifying cultural differences and varying patient acceptance, no consensus can be reached to endorse nurse endoscopists in CRC screening.

CONCLUSIONS

Since the publications of the first Asia Pacific CRC in 2008,[3] there are some countries in this region that endorsed the statements and implemented the screening for colorectal cancers. Compared to the first set of consensus statement, this updated version gives more specific directions on (1) the group of asymptomatic subjects who should receive CRC screening, (2) the preferred choice of screening tools (FIT and colonoscopy in high-risk subjects) and the current status of some screening devices for example, CTC and capsule endoscopy, and (3) the introduction of risk-stratification scoring system in offering early CRC screening by colonoscopy. There is also emphasis on the quality control of the CRC screening programme and address of the use of nurse endoscopists. The target audiences of these consensus statements are practising clinicians. We hope that when the statements are accepted by practitioners in this region they will be able to recommend these to their respective policy-makers. The Asia Pacific Colorectal Cancer Working Group believes that these statements will further enhance the

Downloaded from http://gut.bmj.com/ on March 24, 2015 - Published by group.bmj.com

implementation of CRC screening in the region. These suggestions may also be relevant to CRC screening programmes in other countries outside the Asia Pacific Region.

Author affiliations
[1]Institute of Digestive Disease, The Chinese University of Hong Kong, Shatin, NT, Hong Kong
[2]Department of Medicine and Therapeutics, Chinese University of Hong Kong, Hong Kong, Hong Kong
[3]Department of Internal Medicine, College of Medicine, National Taiwan University, Taipei, Taiwan
[4]Department of Internal Medicine, Yonsei University Wonju College of Medicine, Wonju, Republic of Korea
[5]Endoscopy Division, National Cancer Center Hospital, Tokyo, Japan
[6]Department of Surgery, The Chinese University of Hong Kong, Hong Kong, Hong Kong
[7]Cancer Institute, Zhejiang University, Hanggzhou, Zhejiang, China
[8]Division of Gastroenterology, Bikur Holim Hospital, Jerusalem, Israel
[9]Asian Healthcare Foundation, Asian Institute of Gastroenterology, Hyderabad, Andhra Pradesh, India
[10]Department of Medicine, Asian Healthcare Foundation, National University of Singapore and Senior Consultant Gastroenterologist, Singapore
[11]School of Public Health & Primary Care, The Chinese University of Hong Kong, Hong Kong, Hong Kong
[12]Department of Medicine & Therapeutics, Erasmus University Medical Center, Rotterdam, Netherlands
[13]Institute of Clinical Evaluative Sciences, University of Toronto, Ontario, Canada
[14]Department of Gastroenterology, Flinders Medical Centre, Adelaide, South Australia, Australia
[15]Department of Surgery and Molecular Oncology, University of Dundee, Dundee, UK
[16]Portland VA Medical Centre, Portland, Oregon, USA
[17]Department of Gastroenterology and Hepatology, University of Malaya, Kuala Lumpur, Malaysia

Acknowledgements On behalf of the Asia Pacific Working Group on Colorectal Cancer Screening, we would like to thank the following members for their contributions: Byeon JS, Chen MH, Chong VH, Ho KY, Huang YQ, Kim TI, Lam PY, Leong R, Li J, Makharia G, Payawal D, Quach DT, Rerknimitr R, Sano Y, Wong MCS, Wu DC, Wu KC and Wu MS.

Contributors Study design: JJYS; literature review: JJYS, FKLC and SCN; draft of the manuscript: JJYS and SCN; revision of the manuscript: all authors.

Funding An unrestricted education grant was received from Olympus Medical System Corporation and Given Imaging. In order to avoid conflict of interest, industrial partners were not allowed to provide input for the statements, add references in the literature search, participate in the discussion and vote in the consensus conference. None of the sponsors contributed towards the development of the consensus statements or in their voting.

Competing interests All authors have completed the ICMJE uniform disclosure form at http://www.icmje.org/coi_disclosure.pdf. JJYS, HMC, HSK, TM, SSMG, JYWL, SZ, NR, KGY, KKFT, EJK, LR, GPY, RJS, DL and KLG declare no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work. SCN received grants from Ferring Hong Kong, and Janssen Hong Kong. FKLC received speaker's honorarium from Pfizer Inc., AstraZeneca and Takeda Pharmaceuticals (Hong Kong) Ltd. SA reports personal fees from Given Imaging outside the submitted work. JYLC received speaker's honorarium from Elsai Japan, and travelling support to DDW from Given Imaging (Asia).

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1. Hirabayashi Y, Tanaka S. Comparison of time trends in colorectal cancer incidence (1973–97) in East Asia, Europe and USA, from Cancer Incidence in Five Continents Vol. IV-VIII. *Jpn J Clin Oncol* 2007;37:325–7.
2. Ferlay J, Shin HR, Bray F, *et al*. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer* 2010;127:2893–917.
3. Sung JJ, Lau JY, Young GP, *et al*. Asia Pacific consensus recommendations for colorectal cancer screening. *Gut* 2008;57:1166–76.
4. Rex DK, Johnson DA, Anderson JC, *et al*. American College of Gastroenterology guidelines for colorectal cancer screening 2009 [corrected]. *Am J Gastroenterol* 2009;104:739–50.
5. Cairns SR, Scholefield JH, Steele RJ, *et al*. Guidelines for colorectal cancer screening and surveillance in moderate and high risk groups (update from 2002). *Gut* 2010;59:666–89.
6. Steele RJ, Pox C, Kuipers EJ, *et al*. European guidelines for quality assurance in colorectal cancer screening and diagnosis. First Edition—Management of lesions detected in colorectal cancer screening. *Endoscopy* 2012;44(Suppl 3):SE140–50.
7. Steele RJ, Rey JF, Lambert R. European guidelines for quality assurance in colorectal cancer screening and diagnosis. First Edition—Professional requirements and training. *Endoscopy* 2012;44(Suppl 3):SE106–15.
8. Ferlay J, Bray F, Pisani P, *et al*. *GLOBOCAN 2002: cancer incidence, mortality and prevalence worldwide*. IARC CancerBase No.5, version 2.0. Lyon: IARC Press, 2004.
9. von Karsa L, Patnick J, Segnan N, *et al*. European guidelines for quality assurance in colorectal cancer screening and diagnosis: overview and introduction to the full supplement publication. *Endoscopy* 2013;45:51–9.
10. U.S. Preventive Services Task Force. Screening for colorectal cancer: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med* 2008;149:627–37.
11. Levin B, Lieberman DA, McFarland B, *et al*. Screening and surveillance for the early detection of colorectal cancer and adenomatous polyps, 2008: a joint guideline from the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology. *Gastroenterology* 2008;134:1570–95.
12. Lin OS, Kozarek RA, Schembre DB, *et al*. Screening colonoscopy in very elderly patients: prevalence of neoplasia and estimated impact on life expectancy. *JAMA* 2006;295:2357–65.
13. Sung JJ, Lau JY, Goh KL, *et al*. Increasing incidence of colorectal cancer in Asia: implications for screening. *Lancet Oncol* 2005;6:871–6.
14. Koo JH, Kin S, Wong C, *et al*. Clinical and pathologic outcomes of colorectal cancer in a multi-ethnic population. *Clin Gastroenterol Hepatol* 2008;6:1016–21.
15. Goh KL, Quek KF, Yeo GT, *et al*. Colorectal cancer in Asians: a demographic and anatomic survey in Malaysian patients undergoing colonoscopy. *Aliment Pharmacol Ther* 2005;22:859–64.
16. Ng SC, Lau JY, Chan FK, *et al*. Increased risk of advanced neoplasms among asymptomatic siblings of patients with colorectal cancer. *Gastroenterology* 2013;144:544–50.
17. Tsoi KK, Pau CY, Wu WK, *et al*. Cigarette smoking and the risk of colorectal cancer: a meta-analysis of prospective cohort studies. *Clin Gastroenterol Hepatol* 2009;7:682–8.
18. Renehan AG, Tyson M, Egger M, *et al*. Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. *Lancet* 2008;371:569–78.
19. Ben Q, An W, Jiang Y, *et al*. Body mass index increases risk for colorectal adenomas based on meta-analysis. *Gastroenterology* 2012;142:762–72.
20. Yeoh KG, Ho KY, Chiu HM, *et al*. The Asia-Pacific Colorectal Screening score: a validated tool that stratifies risk for colorectal advanced neoplasia in asymptomatic Asian subjects. *Gut* 2011;60:1236–41.
21. Sung JJY, Chiu HM, Rerknimitr R, *et al*. The Asia Pacific Colorectal Screening scores selects high risk subject for early colonoscopy in colorectal cancer screening: a validation study in asymptomatic subjects. *Gastroenterology* 2013;144:906.
22. Hewitson P, Glasziou P, Watson E, *et al*. Cochrane systematic review of colorectal cancer screening using the fecal occult blood test (hemoccult): an update. *Am J Gastroenterol* 2008;103:1541–9.
23. Allison JE, Tekawa IS, Ransom LJ, *et al*. A comparison of fecal occult-blood tests for colorectal-cancer screening. *N Engl J Med* 1996;334:155–9.
24. Smith A, Young GP, Cole SR, *et al*. Comparison of a brush-sampling fecal immunochemical test for hemoglobin with a sensitive guaiac-based fecal occult blood test in detection of colorectal neoplasia. *Cancer* 2006;107:2152–9.
25. van Rossum LG, van Rijn AF, Laheij RJ, *et al*. Random comparison of guaiac and immunochemical fecal occult blood tests for colorectal cancer in a screening population. *Gastroenterology* 2008;135:82–90.
26. Hol L, van Leerdam ME, van BM, *et al*. Screening for colorectal cancer: randomised trial comparing guaiac-based and immunochemical faecal occult blood testing and flexible sigmoidoscopy. *Gut* 2010;59:62–8.
27. Wong BC, Wong WM, Cheung KL, *et al*. A sensitive guaiac faecal occult blood test is less useful than an immunochemical test for colorectal cancer screening in a Chinese population. *Aliment Pharmacol Ther* 2003;18:941–6.
28. Roslani AC, Abdullah T, Arumugam K. Screening for colorectal neoplasias with fecal occult blood tests: false-positive impact of non-dietary restriction. *Asian Pac J Cancer Prev* 2012;13:237–41.
29. Park DI, Ryu S, Kim YH, *et al*. Comparison of guaiac-based and quantitative immunochemical fecal occult blood testing in a population at average risk undergoing colorectal cancer screening. *Am J Gastroenterol* 2010;105:2017–25.
30. Cole SR, Young GP, Esterman A, *et al*. A randomised trial of the impact of new faecal haemoglobin test technologies on population participation in screening for colorectal cancer. *J Med Screen* 2003;10:117–22.
31. Cole SR, Young GP. Effect of dietary restriction on participation in faecal occult blood test screening for colorectal cancer. *Med J Aust* 2001;175:195–8.
32. Quintero E, Castells A, Bujanda L, *et al*. Colonoscopy versus fecal immunochemical testing in colorectal-cancer screening. *N Engl J Med* 2012;366:697–706.
33. Lane JM, Chow E, Young GP, *et al*. Interval fecal immunochemical testing in a colonoscopic surveillance program speeds detection of colorectal neoplasia. *Gastroenterology* 2010;139:1918–26.

Downloaded from http://gut.bmj.com/ on March 24, 2015 - Published by group.bmj.com

34 Chiang TH, Lee YC, Tu CH, *et al*. Performance of the immunochemical fecal occult blood test in predicting lesions in the lower gastrointestinal tract. *CMAJ* 2011;183:1474–81.
35 Chiu HM, Lee YC, Tu CH, *et al*. Association between early stage colon neoplasms and false-negative results from the fecal immunochemical test. *Clin Gastroenterol Hepatol* 2013;11:832–8.
36 Atkin WS, Edwards R, Kralj-Hans I, *et al*. Once-only flexible sigmoidoscopy screening in prevention of colorectal cancer: a multicentre randomised controlled trial. *Lancet* 2010;375:1624–33.
37 Schoen RE, Pinsky PF, Weissfeld JL, *et al*. Colorectal-cancer incidence and mortality with screening flexible sigmoidoscopy. *N Engl J Med* 2012;366:2345–57.
38 Segnan N, Armaroli P, Bonelli L, *et al*. Once-only sigmoidoscopy in colorectal cancer screening: follow-up findings of the Italian Randomized Controlled Trial-SCORE. *J Natl Cancer* 2011;103:1310–22.
39 Hoff G, Grotmol T, Skovlund E, *et al*. Risk of colorectal cancer seven years after flexible sigmoidoscopy screening: randomised controlled trial. *BMJ* 2009;338: b1846.
40 Elmunzer BJ, Hayward RA, Schoenfeld PS, *et al*. Effect of flexible sigmoidoscopy-based screening on incidence and mortality of colorectal cancer: a systematic review and meta-analysis of randomized controlled trials. *PLoS Med* 2012;9:e1001352.
41 Nishihara R, Wu K, Lochhead P, *et al*. Long-term colorectal-cancer incidence and mortality after lower endoscopy. *N Engl J Med* 2013;369:1095–105.
42 Baxter NN, Goldwasser MA, Paszat LF, *et al*. Association of colonoscopy and death from colorectal cancer. *Ann Intern Med* 2009;150:1–8.
43 Baxter NN, Warren JL, Barrett MJ, *et al*. Association between colonoscopy and colorectal cancer mortality in a US cohort according to site of cancer and colonoscopist specialty. *J Clin Oncol* 2012;30:2664–9.
44 Lieberman D. Progress and challenges in colorectal cancer screening and surveillance. *Gastroenterology* 2010;138:2115–26.
45 Zauber AG, Winawer SJ, O'Brien MJ, *et al*. Colonoscopic polypectomy and long-term prevention of colorectal-cancer deaths. *N Engl J Med* 2012;366:687–96.
46 Rabeneck L, Paszat LF, Saskin R, *et al*. Association between colonoscopy rates and colorectal cancer mortality. *Am J Gastroenterol* 2010;105:1627–32.
47 Singh H, Nugent Z, Demers AA, *et al*. The reduction in colorectal cancer mortality after colonoscopy varies by site of the cancer. *Gastroenterology* 2010;139:1128–37.
48 Kim DH, Pickhardt PJ, Taylor AJ, *et al*. CT colonography versus colonoscopy for the detection of advanced neoplasia. *N Engl J Med* 2007;357:1403–12.
49 Pickhardt PJ, Hassan C, Halligan S, *et al*. Colorectal cancer: CT colonography and colonoscopy for detection—systematic review and meta-analysis. *Radiology* 2011;259:393–405.
50 de Haan MC, van Gelder RE, Graser A, *et al*. Diagnostic value of CT-colonography as compared to colonoscopy in an asymptomatic screening population: a meta-analysis. *Eur Radiol* 2011;21:1747–63.
51 van DL, de Wijkerslooth TR, de Haan MC, *et al*. Time requirements and health effects of participation in colorectal cancer screening with colonoscopy or computed tomography colonography in a randomized controlled trial. *Endoscopy* 2013;45:182–8.
52 de Wijkerslooth TR, de Haan MC, Stoop EM, *et al*. Burden of colonoscopy compared to non-cathartic CT-colonography in a colorectal cancer screening programme: randomised controlled trial. *Gut* 2012;61:1552–9.
53 Stoop EM, de Haan MC, de Wijkerslooth TR, *et al*. Participation and yield of colonoscopy versus non-cathartic CT colonography in population-based screening for colorectal cancer: a randomised controlled trial. *Lancet Oncol* 2012;13:55–64.
54 Lucidarme O, Cadi M, Berger G, *et al*. Cost-effectiveness modeling of colorectal cancer: computed tomography colonography vs colonoscopy or fecal occult blood tests. *Eur J Radiol* 2012;81:1413–19.
55 Pickhardt PJ. Polyp detection at CT colonography: inadequate primary 3D endoluminal reference standard precludes meaningful comparison. *Radiology* 2007;244:316–17.
56 Sung JJ, Luo DJ, Ng SS, *et al*. Patients with polyps larger than 5 mm in computed tomography colonoscopy screening have high risk for advanced colonic neoplasia in Asia. *Clin Gastroenterol Hepatol* 2011;9:47–51.
57 Van GA, Munoz-Navas M, Fernandez-Urien I, *et al*. Capsule endoscopy versus colonoscopy for the detection of polyps and cancer. *N Engl J Med* 2009;361:264–70.
58 Eliakim R, Yassin K, Niv Y, *et al*. Prospective multicenter performance evaluation of the second-generation colon capsule compared with colonoscopy. *Endoscopy* 2009;41:1026–31.
59 Spada C, Hassan C, Munoz-Navas M, *et al*. Second-generation colon capsule endoscopy compared with colonoscopy. *Gastrointest Endosc* 2011;74:581–9.
60 Rex DK, Adler SN, Burch WC. Accuracy of PillCam COLON 2 for detecting subjects with Adenomas >6 mm. *Gastroenterology* 2013;144:907.
61 Spada C, Hassan C, Galmiche JP, *et al*. Colon capsule endoscopy: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. *Endoscopy* 2012;44:527–36.
62 Jasperson KW, Tuohy TM, Neklason DW, *et al*. Hereditary and familial colon cancer. *Gastroenterology* 2010;138:2044–58.
63 Johns LE, Kee F, Collins BJ, *et al*. Colorectal cancer mortality in first-degree relatives of early-onset colorectal cancer cases. *Dis Colon Rectum* 2002;45:681–6.
64 Fuchs CS, Giovannucci EL, Colditz GA, *et al*. A prospective study of family history and the risk of colorectal cancer. *N Engl J Med* 1994;331:1669–74.
65 Johns LE, Houlston RS. A systematic review and meta-analysis of familial colorectal cancer risk. *Am J Gastroenterol* 2001;96:2992–3003.
66 Butterworth AS, Higgins JP, Pharoah P. Relative and absolute risk of colorectal cancer for individuals with a family history: a meta-analysis. *Eur J Cancer* 2006;42:216–27.
67 Baglietto L, Jenkins MA, Severi G, *et al*. Measures of familial aggregation depend on definition of family history: meta-analysis for colorectal cancer. *J Clin Epidemiol* 2006;59:114–24.
68 Austin GL, Goldstein JI, Peters SL, *et al*. Are colorectal cancer screening recommendations for first-degree relatives of patients with adenomas too aggressive? *Clin Gastroenterol Hepatol* 2011;9:308–13.
69 Tung SY, Wu CS. Risk factors for colorectal adenomas among immediate family members of patients with colorectal cancer in Taiwan: a case-control study. *Am J Gastroenterol* 2000;95:3624–8.
70 Wong MC, Tsoi KK, Ng SS, *et al*. A comparison of the acceptance of immunochemical faecal occult blood test and colonoscopy in colorectal cancer screening: a prospective study among Chinese. *Aliment Pharmacol Ther* 2010;32:74–82.
71 Wong MC, Ching JY, Hirai HH, *et al*. Perceived obstacles of Colorectal cancer screening and their associated factors among 10,078 Chinese participants. *PLoS ONE* 2013;8:e70209.
72 Liou JM, Lin JT, Huang SP, *et al*. Screening for colorectal cancer in average-risk Chinese population using a mixed strategy with sigmoidoscopy and colonoscopy. *Dis Colon Rectum* 2007;50:630–40.
73 Rex DK, Kahi CJ, Levin B, *et al*. Guidelines for colonoscopy surveillance after cancer resection: a consensus update by the American Cancer Society and the US Multi-Society Task Force on Colorectal Cancer. *Gastroenterology* 2006;130:1865–71.
74 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.
75 Chung SJ, Kim YS, Yang SY, *et al*. Five-year risk for advanced colorectal neoplasia after initial colonoscopy according to the baseline risk stratification: a prospective study in 2452 asymptomatic Koreans. *Gut* 2011;60:1537–43.
76 Imperiale TF, Glowinski EA, Lin-Cooper C, *et al*. Five-year risk of colorectal neoplasia after negative screening colonoscopy. *N Engl J Med* 2008;359:1218–24.
77 Lieberman DA, Weiss DG, Harford WV, *et al*. Five-year colon surveillance after screening colonoscopy. *Gastroenterology* 2007;133:1077–85.
78 Leung WK, Lau JY, Suen BY, *et al*. Repeat-screening colonoscopy 5 years after normal baseline-screening colonoscopy in average-risk Chinese: a prospective study. *Am J Gastroenterol* 2009;104:2028–34.
79 Brenner H, Chang-Claude J, Seiler CM, *et al*. Long-term risk of colorectal cancer after negative colonoscopy. *J Clin Oncol* 2011;29:3761–7.
80 Brenner H, Chang-Claude J, Seiler CM, *et al*. Protection from colorectal cancer after colonoscopy: a population-based, case-control study. *Ann Intern Med* 2011;154:22–30.
81 Singh H, Turner D, Xue L, *et al*. Colonoscopic screening for colorectal cancer. *JAMA* 2006;296:2438–9.
82 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.
83 van Heijningen EM, Lansdorp-Vogelaar I, Kuipers EJ, *et al*. Features of adenoma and colonoscopy associated with recurrent colorectal neoplasia based on a large community-based study. *Gastroenterology* 2013;144:1410–18.
84 Baxter NN, Sutradhar R, Forbes SS, *et al*. Analysis of administrative data finds endoscopist quality measures associated with postcolonoscopy colorectal cancer. *Gastroenterology* 2011;140:65–72.
85 Farrar WD, Sawhney MS, Nelson DB, *et al*. Colorectal cancers found after a complete colonoscopy. *Clin Gastroenterol Hepatol* 2006;4:1259–64.
86 Bressler B, Paszat LF, Chen Z, *et al*. Rates of new or missed colorectal cancers after colonoscopy and their risk factors: a population-based analysis. *Gastroenterology* 2007;132:96–102.
87 Singh H, Nugent Z, Demers AA, *et al*. Rate and predictors of early/missed colorectal cancers after colonoscopy in Manitoba: a population-based study. *Am J Gastroenterol* 2010;105:2588–96.
88 Shaukat A, Arain M, Thaygarajan B, *et al*. Is BRAF mutation associated with interval colorectal cancers? *Dig Dis Sci* 2010;55:2352–6.
89 Arain MA, Sawhney M, Sheikh S, *et al*. CIMP status of interval colon cancers: another piece to the puzzle. *Am J Gastroenterol* 2010;105:1189–95.
90 Sawhney MS, Farrar WD, Gudiseva S, *et al*. Microsatellite instability in interval colon cancers. *Gastroenterology* 2006;131:1700–5.
91 Kaminski MF, Regula J, Kraszewska E, *et al*. Quality indicators for colonoscopy and the risk of interval cancer. *N Engl J Med* 2010;362:1795–803.
92 Williams JE, Le TD, Faigel DO. Polypectomy rate as a quality measure for colonoscopy. *Gastrointest Endosc* 2011;73:498–506.
93 Adler A, Lieberman D, Aminalai A, *et al*. Data quality of the German screening Colonoscopy registry. *Endoscopy* 2013;45:813–18.

Downloaded from http://gut.bmj.com/ on March 24, 2015 - Published by group.bmj.com

94 Harewood GC, Sharma VK, de GP. Impact of colonoscopy preparation quality on detection of suspected colonic neoplasia. *Gastrointest Endosc* 2003;58:76–9.
95 Rostom A, Jolicoeur E, Dube C, *et al*. A randomized prospective trial comparing different regimens of oral sodium phosphate and polyethylene glycol-based lavage solution in the preparation of patients for colonoscopy. *Gastrointest Endosc* 2006;64:544–52.
96 Barclay RL, Vicari JJ, Greenlaw RL. Effect of a time-dependent colonoscopic withdrawal protocol on adenoma detection during screening colonoscopy. *Clin Gastroenterol Hepatol* 2008;6:1091–8.
97 Barclay RL, Vicari JJ, Doughty AS, *et al*. Colonoscopic withdrawal times and adenoma detection during screening colonoscopy. *N Engl J Med* 2006;355:2533–41.
98 Lee TJ, Blanks RG, Rees CJ, *et al*. Longer mean colonoscopy withdrawal time is associated with increased adenoma detection: evidence from the Bowel Cancer Screening Programme in England. *Endoscopy* 2013;45:20–6.
99 Jover R, Zapater P, Polania E, *et al*. Modifiable endoscopic factors that influence the adenoma detection rate in colorectal cancer screening colonoscopies. *Gastrointest Endosc* 2013;77:381–9.
100 Rex DK, Petrini JL, Baron TH, *et al*. Quality indicators for colonoscopy. *Am J Gastroenterol* 2006;101:873–85.
101 Beaulieu D, Barkun A, Martel M. Quality audit of colonoscopy reports amongst patients screened or surveilled for colorectal neoplasia. *World J Gastroenterol* 2012;18:3551–7.
102 Gavin DR, Valori RM, Anderson JT, *et al*. The national colonoscopy audit: a nationwide assessment of the quality and safety of colonoscopy in the UK. *Gut* 2013;62:242–9.
103 Subramanian V, Mannath J, Hawkey CJ, *et al*. High definition colonoscopy vs. standard video endoscopy for the detection of colonic polyps: a meta-analysis. *Endoscopy* 2011;43:499–505.
104 Adler A, Aminalai A, Aschenbeck J, *et al*. Latest generation, wide-angle, high-definition colonoscopes increase adenoma detection rate. *Clin Gastroenterol Hepatol* 2012;10:155–9.
105 Kahi CJ, Anderson JC, Waxman I, *et al*. High-definition chromocolonoscopy vs. high-definition white light colonoscopy for average-risk colorectal cancer screening. *Am J Gastroenterol* 2010;105:1301–7.
106 Pohl J, Schneider A, Vogell H, *et al*. Pancolonic chromoendoscopy with indigo carmine versus standard colonoscopy for detection of neoplastic lesions: a randomised two-centre trial. *Gut* 2011;60:485–90.
107 Brown SR, Baraza W. Chromoscopy versus conventional endoscopy for the detection of polyps in the colon and rectum. *Cochrane Database Syst Rev* 2010;(10):CD006439.
108 McGill SK, Evangelou E, Ioannidis JP, *et al*. Narrow band imaging to differentiate neoplastic and non-neoplastic colorectal polyps in real time: a meta-analysis of diagnostic operating characteristics. *Gut* 2013;62:1704–13.
109 Pasha SF, Leighton JA, Das A, *et al*. Comparison of the yield and miss rate of narrow band imaging and white light endoscopy in patients undergoing screening or surveillance colonoscopy: a meta-analysis. *Am J Gastroenterol* 2012;107:363–70.
110 Nagorni A, Bjelakovic G, Petrovic B. Narrow band imaging versus conventional white light colonoscopy for the detection of colorectal polyps. *Cochrane Database Syst Rev* 2012;1:CD008361.
111 Hong SN, Choe WH, Lee JH, *et al*. Prospective, randomized, back-to-back trial evaluating the usefulness of i-SCAN in screening colonoscopy. *Gastrointest Endosc* 2012;75:1011–21.
112 Chung SJ, Kim D, Song JH, *et al*. Efficacy of computed virtual chromoendoscopy on colorectal cancer screening: a prospective, randomized, back-to-back trial of Fuji Intelligent Color Enhancement versus conventional colonoscopy to compare adenoma miss rates. *Gastrointest Endosc* 2010;72:136–42.
113 Pohl J, Lotterer E, Balzer C, *et al*. Computed virtual chromoendoscopy versus standard colonoscopy with targeted indigocarmine chromoscopy: a randomised multicentre trial. *Gut* 2009;58:73–8.
114 Takeuchi Y, Inoue T, Hanaoka N, *et al*. Autofluorescence imaging with a transparent hood for detection of colorectal neoplasms: a prospective, randomized trial. *Gastrointest Endosc* 2010;72:1006–13.
115 Ramsoekh D, Haringsma J, Poley JW, *et al*. A back-to-back comparison of white light video endoscopy with autofluorescence endoscopy for adenoma detection in high-risk subjects. *Gut* 2010;59:785–93.
116 Ng SC, Tsoi KK, Hirai HW, *et al*. The efficacy of cap-assisted colonoscopy in polyp detection and cecal intubation: a meta-analysis of randomized controlled trials. *Am J Gastroenterol* 2012;107:1165–73.
117 Leufkens AM, DeMarco DC, Rastogi A, *et al*. Effect of a retrograde-viewing device on adenoma detection rate during colonoscopy: the TERRACE study. *Gastrointest Endosc* 2011;73:480–9.
118 Siersema PD, Rastogi A, Leufkens AM, *et al*. Retrograde-viewing device improves adenoma detection rate in colonoscopies for surveillance and diagnostic workup. *World J Gastroenterol* 2012;18:3400–8.
119 Maule WF. Screening for colorectal cancer by nurse endoscopists. *N Engl J Med* 1994;330:183–7.
120 van Putten PG, Ter Borg F, Adang RP, *et al*. Nurse endoscopists perform colonoscopies according to the international standard and with high patient satisfaction. *Endoscopy* 2012;44:1127–32.
121 Swarbrick E, Harnden S, Hodson R, *et al*. bsg.org.uk/clinical.guideline
122 Davila RE, Rajan E, Baron TH, *et al*. ASGE guideline: colorectal cancer screening and surveillance. *Gastrointest Endosc* 2006;63:546–57.
123 Limoges-Gonzalez M, Mann NS, Al-Juburi A, *et al*. Comparisons of screening colonoscopy performed by a nurse practitioner and gastroenterologists: a single-center randomized controlled trial. *Gastroenterol Nurs* 2011;34:210–16.
124 Lieberman D. How good is your dentist? How good is your endoscopist? The quality imperative. *Gastroenterology* 2012;142:194–6.

Downloaded from http://gut.bmj.com/ on March 24, 2015 - Published by group.bmj.com

An updated Asia Pacific Consensus Recommendations on colorectal cancer screening

J J Y Sung, S C Ng, F K L Chan, H M Chiu, H S Kim, T Matsuda, S S M Ng, J Y W Lau, S Zheng, S Adler, N Reddy, K G Yeoh, K K F Tsoi, J Y L Ching, E J Kuipers, L Rabeneck, G P Young, R J Steele, D Lieberman and K L Goh

Gut 2015 64: 121-132 originally published online March 19, 2014
doi: 10.1136/gutjnl-2013-306503

Updated information and services can be found at:
http://gut.bmj.com/content/64/1/121

These include:

References This article cites 118 articles, 19 of which you can access for free at:
http://gut.bmj.com/content/64/1/121#BIBL

Email alerting service Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Topic Collections Articles on similar topics can be found in the following collections

Colon cancer (1472)
Endoscopy (975)

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/

Roles of the *ALDH2* and *ADH1B* Genotypes on the Association Between Alcohol Intake and Serum Adiponectin Levels Among Japanese Male Workers

Shinya Maeda, Kanae Mure, Kouichi Mugitani, Yutaka Watanabe, Masataka Iwane, Osamu Mohara, and Tatsuya Takeshita

Background: Adiponectin secreted from adipose tissue is assumed to mediate protective effects on development of metabolic syndrome (MetS) and MetS-related diseases such as cardiovascular diseases and cancer. Relationship between alcohol intake and circulating adiponectin levels is not consistent among the several previous studies. In the present study, we investigated effects of alcohol intake and the alcohol-related polymorphisms on serum adiponectin levels among Japanese male workers.

Methods: We conducted a cross-sectional design study with 541 male workers aged 51.5 ± 5.9 (mean ± SD) years in a Japanese plant. Information on alcohol intake and other lifestyles was obtained by a self-administered questionnaire. Serum total adiponectin (T-Ad), high-molecular-weight adiponectin (HMW-Ad), medium-molecular-weight adiponectin (MMW-Ad), and low-molecular-weight adiponectin (LMW-Ad) levels were measured by the enzyme-linked immune assay system kit. Two genotypes in the alcohol dehydrogenase-1B (*ADH1B*) and aldehyde dehydrogenase-2 (*ALDH2*) genes were determined using blood sample. In multivariate regression analyses, we adjusted for age, body mass index, smoking, and physical exercise.

Results: Among all subjects, high alcohol consumption of 12 units (1 unit contains 22.9 g of ethanol) a week or more was negatively associated with T-Ad levels in the multivariate model, although not significant. When we performed analyses separately for each genotype, high alcohol consumption was negatively associated with T-Ad, HMW-Ad, and LMW-Ad levels only in those with *ADH1B *2/*2*. Such relationships were not observed in each *ALDH2* genotype group.

Conclusions: High alcohol consumption was inversely associated with T-Ad, HMW-Ad, and LMW-Ad levels in those with *ADH1B *2/*2* genotype, but not in those with the other *ADH1B* genotypes. To our knowledge, this is the first study that reports combined effects of the alcohol-related polymorphisms and alcohol intake on serum adiponectin levels. Additional studies are required to confirm the present finding.

Key Words: Adiponectin, Alcohol Intake, Alcohol Dehydrogenase-1B, Aldehyde Dehydrogenase-2, Acetaldehyde.

METABOLIC SYNDROME (METS) has become a major worldwide public health problem (Ford, 2005). MetS is known to promote the development of cardiovascular diseases (Iso et al., 2007). In Japan, the prevalence of MetS has been increasing particularly among men in recent years (Anonymous, 2013). Among Japanese aged 20 or over, 28.8% of men and 10.4% of women met the criteria for MetS in 2011 (Anonymous, 2013).

Adipokines secreted from adipose tissue have an important role in the pathogenesis of MetS (Matsuzawa, 2010; Matsuzawa et al., 2011). Pro-inflammatory cytokines, such as tumor necrosis factor-α (TNF-α), plasminogen activator inhibitor type 1, and interleukin-6, contribute to the pathophysiology of MetS (Aprahamian and Sam, 2011). On the other hand, adiponectin (Matsuzawa, 2010; Matsuzawa et al., 2011), one of important adipokines, inhibits the expression of TNF-α in adipose tissue and mediates protective effects in the pathogenesis of MetS (Aprahamian and Sam, 2011). Hypoadiponectinemia has been demonstrated to be related to MetS, cardiovascular disease (Matsuzawa, 2010; Matsuzawa et al., 2011; Pischon et al., 2004), and breast and colon cancer (Gulcelik et al., 2012; Matsuzawa, 2010). Furthermore, plasma levels of high-molecular-weight adiponectin (HMW-Ad), 1 of the 3 adiponectin forms, have also been associated with type 2 diabetes (Heidemann et al., 2008) and coronary heart disease (Pischon et al., 2011).

Several previous studies have shown that moderate alcohol intake is associated with elevated serum adiponectin

From the Department of Public Health (SM, KMur, TT), Wakayama Medical University School of Medicine, Wakayama, Japan; and Wakayama Wellness Foundation (SM, KMug, YW, MI, OM), Wakayama, Japan.

Received for publication November 1, 2013; accepted February 10, 2014.

Reprint requests: Tatsuya Takeshita, MD, PhD, Department of Public Health, Wakayama Medical University School of Medicine, 811-1 Kimiidera, Wakayama 641-8509, Japan; Tel.: +81-73-441-0647; Fax: +81-73-448-0238; E-mail: ttakeshi@wakayama-med.ac.jp

Copyright © 2014 by the Research Society on Alcoholism.

DOI: 10.1111/acer.12406

levels (Kotani et al., 2007; Pischon et al., 2005). In contrast, other recent studies have shown that alcohol intake and either serum adiponectin levels (Nishise et al., 2010) or serum HMW-Ad levels (Kawamoto et al., 2010) are inversely associated in Japanese men.

Ethanol (EtOH) is initially oxidized to acetaldehyde by alcohol dehydrogenase (ADH), and acetaldehyde is subsequently oxidized into acetic acid, mainly by aldehyde dehydrogenase-2 (ALDH2) (Lieber, 1995). Asians have several frequent polymorphisms in these alcohol-metabolizing enzyme genes including *ALDH2* and alcohol dehydrogenase-1B (*ADH1B)*, which are associated with alcohol sensitivity, alcohol drinking habits (Macgregor et al., 2009; Takeshita et al., 1994; Tsuchihashi-Makaya et al., 2009), and alcohol-related health problems (Higuchi et al., 1995; Yokoyama et al., 1996). The variant *ALDH2*2* allele carriers have higher blood acetaldehyde concentrations after drinking alcohol because of the lower ALDH2 activity (Enomoto et al., 1991). Those with the *ALDH2*1/*2* genotype have higher risk for esophageal cancer (Yang et al., 2010; Yokoyama et al., 2002) and alcohol-induced bronchial asthma (Matsuse et al., 2001). The variant *ADH1B* genotypes have higher enzyme activity, produce acetaldehyde more rapidly than the wild *ADH1B* genotype (Yin et al., 1984), and show higher alcohol sensitivity (Macgregor et al., 2009; Takeshita et al., 1996, 2001). Higher risk for both alcoholism and esophageal cancer has been reported for the wild *ADH1B* genotype (Chen et al., 1999; Yang et al., 2010; Yokoyama et al., 2002), while relationships between the *ADH1B* genotypes and other alcohol-related health problems have not been well understood yet.

To our knowledge, there have been no published reports that describe the association between alcohol consumption and serum adiponectin levels among those with different genotypes of *ADH1B* and *ALDH2*. In the present study, we examined the effects of both *ALDH2* and *ADH1B* genotypes and alcohol intake on serum adiponectin levels, including the 3 different molecular weight forms, among male workers in a Japanese plant.

MATERIALS AND METHODS

Subjects

Subjects were workers from a metal plant in Japan with 2,207 male and 40 female workers. Of 2,247 subjects, 731 (699 men and 32 women) gave a written informed consent to participate the present investigation including identification of the genotypes (response rate: 32.5%). Those who had taken medications for hypertension, diabetes, dyslipidemia, cardiovascular or cerebrovascular diseases, or who did not completely answer a self-administered questionnaire during an annual health examination in 2006 were excluded. Women were also excluded because of the small sample size. Thus, 541 men, aged 51.5 ± 5.9 (mean ± SD) years, were included in the present analysis. All records and results were kept confidential. Prior to recruiting subjects, the present study was approved by the ethical committee for analytical research on the human genome of Wakayama Medical University (Approval No. 44).

Alcohol Intake, Smoking, and Physical Exercise

Information on drinking frequency, amounts of alcohol consumption per week, smoking, and physical exercise was collected using a self-administered questionnaire.

Regarding "alcohol intake," the amount is often expressed using the units in Japan. One unit (180 ml or 1 traditional container) of Japanese sake (Japanese rice wine) contains 22.9 g of EtOH. A nondrinker was defined as a subject who had never or had rarely drunk (<1 unit a week on average). There were 4 response choices for amounts of alcohol consumption: 1, 2, 3, or 4 units a day or more. There were 8 choices for drinking frequency: 0, 1, 2, 3, 4, 5, 6, or 7 days a week. The subjects were classified into 3 alcohol consumption groups by setting cutoff points at the 33rd (4 units a week) and the 67th (11 units a week) percentile points in the subjects. The 3 groups were designated as low (0 to 4 units a week), intermediate (5 to 11 units a week), or high (12 units a week or more) alcohol consumption group.

For smoking habit, there were 5 choices: have never smoked, do not smoke now, 20, 21 to 40, or 41 cigarettes a day or more. Smoking habits were categorized into 2 groups; nonsmokers/ex-smokers and current smokers. There were 5 choices for the frequency of physical exercise for more than 30 minutes per day: every day, 2 to 4 days a week, once a week, once a month, or do not exercise. Physical exercise was also categorized into 2 groups, that is, less than once a week or once a week or more. We also asked medication use for hypertension, diabetes, dyslipidemia, cardiovascular or cerebrovascular diseases by 2 choices: yes or no.

Serum Adiponectin Levels

Serum adiponectin levels were assessed by an enzyme-linked immune assay system (Sekisui Medical, Tokyo, Japan). The total adiponectin (T-Ad), HMW-Ad, and the combination of HMW-Ad and medium-molecular-weight adiponectin (MMW-Ad) levels were measured directly by this system. The MMW-Ad level was calculated by subtracting the HMW-Ad level from the mixture of HMW-Ad and MMW-Ad levels. The low-molecular-weight adiponectin (LMW-Ad) level was calculated by subtracting the mixture of HMW-Ad and MMW-Ad levels from the T-Ad level.

ALDH2 *Genotype*

Genomic DNA was isolated from peripheral blood using QIAamp Blood DNA Mini Kit (Qiagen, Germantown, MD) according to the manufacturer's instruction. For detecting *ALDH2* Glu504Lys genotype (rs 671), 2 allele-specific primer sets and 20 to 30 ng DNA were used in total 25 μl polymerase chain reaction (PCR) mixture (1.5 μl of 2 mM dNTPs, 1 μl of each primers, 0.5 units of AmpliTaq Gold [Applied Biosystems, Carlsbad, CA], 2.5 μl of X10 PCR Master Mix [Applied Biosystems] containing 15 mM $MgCl_2$). Sequences of sense (F1) and antisense (R1) primers for the Glu allele were 5′-TCA TGC CAT GGC AAC TCC AGC-3′ and 5′-CCC ACA CTC ACA GTT TTC TCT TC-3′, and sequences of sense (F2) and antisense (R2) primers for the Lys allele were 5′-TAC GGG CTG CAG GCA TAC ACT A-3′ and 5′-TGA TCC CCA GCA GGT CCT GAA-3′. PCR was conducted as follows: 5 minutes of initial denaturation at 95°C; then 30 cycles of 1 minute at 95°C, 1 minute at 60°C, and 1 minute at 72°C; and a 5-minute final extension at 72°C.

ADH1B *Genotype*

Following *ADH1B* (rs 1229984), genotyping steps were performed with reagents and kits obtained from Applied Biosystems. Each assay was carried out using 20 ng DNA in a 25-μl reaction containing a TaqMan Genotyping Master Mix, forward and reverse primers, and FAM- and VIC-labeled probes. Allelic discrimination

was detected by 7300 Real-Time PCR System (Applied Biosystems) using Sequence Detection System Software (Applied Biosystems).

Statistical Analysis

Data are summarized as means and standard deviations, as median (25th to 75th percentile), or as percentage values. Differences in mean age, mean body mass index (BMI), and the means for logarithmic values of T-Ad, HMW-Ad, MMW-Ad, and LMW-Ad levels across the different *ALDH2* and *ADH1B* genotypes were tested using analysis of variance (ANOVA) with Bonferroni's correction. Differences in alcohol consumption were tested using Kruskal–Wallis test. Proportions of cigarette smoking and physical exercise were tested using the chi-squared test.

Differences in the means for logarithmic values of T-Ad levels across different levels of age, smoking habit, or physical exercise were tested using *t*-test. Differences in the means for logarithmic values of T-Ad levels across different levels of BMI or alcohol consumption were tested by ANOVA with Dunnett's correction.

The association between alcohol consumption and logarithmic values of T-Ad, HMW-Ad, MMW-Ad, and LMW-Ad levels was evaluated by regression analysis. In the multivariate models, we adjusted for age, BMI, smoking, and physical exercise. All statistical analyses were performed with SPSS version 15.0 (SPSS, Chicago, IL). A p-value of <0.05 was considered statistically significant.

RESULTS

The frequencies of the 3 *ALDH2* genotypes in the subjects are shown in Table 1. The proportion of those with the *ALDH2*1/*1*, *ALDH2*1/*2*, and *ALDH2*2/*2* genotypes among the study subjects were 299/541 (55.3%), 191/541 (35.3%), and 51/541 (9.4%), respectively. Hardy–Weinberg's prediction was statistically significant ($\chi^2 = 6.15$, $p < 0.05$). The frequencies of the 3 *ADH1B* genotypes in the subjects are shown in Table 1. The proportion of those with the *ADH1B*1/*1*, *ADH1B*1/*2*, and *ADH1B *2/*2* genotypes among the study subjects were 29/541 (5.4%), 200/541 (37.0%), and 312/541 (57.7%), respectively. Hardy–Weinberg's prediction was not statistically significant ($\chi^2 = 0.186$).

The characteristics of the subjects according to the *ALDH2* and *ADH1B* genotypes are shown in Table 1. There were no significant differences in age, BMI, T-Ad, HMW-Ad, MMW-Ad, LMW-Ad levels, or proportions of the smokers between the 3 *ALDH2* genotypes. Amounts of alcohol consumption were significantly different between the 3 *ALDH2* genotypes. The physical activity level was significantly lower in the *ALDH2*2/*2* group than that in the *ALDH2*1/*1* group ($p < 0.05$).

There were no significant differences in BMI, T-Ad, HMW-Ad, MMW-Ad, LMW-Ad levels, proportions of the smokers, physical activity level, and amounts of alcohol consumption between the 3 *ADH1B* genotypes. Those with *ADH1B*1/*2* were significantly older than those with *ADH1B*1/*1* ($p < 0.05$).

The relationship between confounding factors and T-Ad levels among the *ALDH2* or *ADH1B* genotypes is shown in Table 2 or Table 3, respectively. The drinking group of 12 units a week or more had tendencies to have lower T-Ad levels than that of 0 to 4 units a week in those with the

Table 1. Characteristics Among the Different *ALDH2* and *ADH1B* Genotypes

		ALDH2			*ADH1B*		
	All (n = 541)	**1/*1* (n = 299)	**1/*2* (n = 191)	**2/*2* (n = 51)	**1/*1* (n = 29)	**1/*2* (n = 200)	**2/*2* (n = 312)
Age (years), mean (SD)	51.5 (5.9)	51.5 (5.8)	51.5 (6.0)	51.3 (5.7)	48.7 (7.2)	51.9* (5.6)	51.4 (5.9)
BMI (kg/m^2), mean (SD)	23.5 (2.7)	23.6 (2.6)	23.4 (2.6)	23.7 (3.1)	23.8 (2.7)	23.4 (2.6)	23.6 (2.7)
T-Ad (μg/ml), median (IQR)	4.51 (3.38 to 5.92)	4.42 (3.35 to 5.65)	4.54 (3.46 to 6.02)	4.85 (3.48 to 6.70)	4.81 (3.84 to 5.85)	4.48 (3.36 to 5.79)	4.44 (3.32 to 5.95)
HMW-Ad (μg/ml), median (IQR)	1.76 (1.09 to 2.64)	1.70 (1.09 to 2.51)	1.82 (1.06 to 2.80)	1.84 (1.14 to 3.26)	1.87 (1.35 to 2.58)	1.73 (1.06 to 2.50)	1.76 (1.09 to 2.75)
MMW-Ad (μg/ml), median (IQR)	1.03 (0.78 to 1.39)	1.03 (0.77 to 1.41)	1.03 (0.80 to 1.38)	1.04 (0.83 to 1.36)	1.13 (0.87 to 1.68)	1.05 (0.78 to 1.43)	1.02 (0.77 to 1.32)
LMW-Ad (μg/ml), median (IQR)	1.65 (1.32 to 2.01)	1.63 (1.32 to 2.02)	1.69 (1.30 to 2.00)	1.78 (1.35 to 2.13)	1.75 (1.34 to 2.05)	1.64 (1.32 to 1.98)	1.65 (1.29 to 2.02)
Alcohol consumption (unit a week),[a] median (IQR)	7 (2 to 14)	10 (6 to 14)	4** (0 to 7)	0** (0 to 0)	7 (3.5 to 14)	7 (3 to 14)	7 (1 to 12)
Smoking							
Current smokers, n (%)	247 (45.7)	139 (46.5)	83 (43.5)	25 (49.0)	13 (44.8)	91 (45.5)	143 (45.8)
Physical exercise							
≥once a week, n (%)	244 (45.1)	150 (50.2)	78 (40.8)	16*** (31.4)	12 (41.4)	86 (43.0)	146 (46.8)

SD, standard deviation; BMI, body mass index; IQR, interquartile range; T-Ad, serum total adiponectin; HMW-Ad, serum high-molecular-weight adiponectin; MMW-Ad, serum medium-molecular-weight adiponectin; LMW-Ad, serum low-molecular-weight adiponectin.
[a]1 unit corresponds to 22.9 g ethanol.
*$p < 0.05$ vs. *ADH1B*1/*1* for ANOVA with Bonferroni correction. **$p < 0.001$, ***$p < 0.05$ vs. *ALDH2*1/*1* for the Kruskal–Wallis test, or chi-squared test.

Table 2. Relationship Between Confounding Factors and T-Ad Among the *ALDH2* Genotypes

	All (n = 541)		*ALDH2*					
			*1/*1 (n = 299)		*1/*2 (n = 191)		*2/*2 (n = 51)	
	median (IQR)	n	Median (IQR)	n	Median (IQR)	n	Median (IQR)	n
Age (years)								
<50	4.49 (3.27 to 5.95)	178	4.32 (3.20 to 5.78)	92	4.63 (3.47 to 6.06)	69	5.50 (2.92 to 6.86)	17
≥50	4.51 (3.44 to 5.91)	363	4.48 (3.35 to 5.65)	207	4.39 (3.42 to 6.02)	122	4.83 (3.67 to 6.28)	34
BMI (kg/m^2)								
<22.0	5.23 (3.68 to 6.94)	163	4.67 (3.44 to 6.53)	87	5.53 (4.09 to 7.19)	62	5.84 (4.86 to 7.29)	14
22.0 to 25.0	4.41* (3.37 to 5.59)	227	4.52 (3.49 to 5.72)	125	4.28* (3.24 to 5.24)	83	4.43 (2.78 to 6.70)	19
≥25.0	3.92* (3.09 to 5.13)	151	3.92** (3.10 to 5.13)	87	3.86* (2.98 to 5.05)	46	4.39 (3.44 to 5.60)	18
Alcohol consumption (unit a week)								
0 to 4	4.45 (3.38 to 5.94)	186	4.41 (3.44 to 5.98)	43	4.34 (3.23 to 5.61)	96	4.61 (3.31 to 6.60)	47
5 to 11	4.83 (3.60 to 6.10)	178	4.61 (3.45 to 6.03)	113	5.01 (3.76 to 6.19)	63		2
≥12	4.36 (3.19 to 5.53)	177	4.36 (3.19 to 5.49)	143	4.11 (2.97 to 5.72)	32		2
Smoking habit								
Never or Former	4.77 (3.49 to 6.06)	294	4.68 (3.44 to 5.99)	160	4.69 (3.58 to 6.08)	108	5.24 (3.40 to 6.86)	26
Current	4.20*** (3.23 to 5.49)	247	4.11 (3.19 to 5.41)	139	4.24 (3.22 to 5.78)	83	4.51 (3.40 to 6.00)	25
Physical exercise								
<once a week	4.51 (3.26 to 5.93)	297	4.42 (3.34 to 5.85)	149	4.48 (3.22 to 5.82)	113	5.15 (3.50 to 6.84)	35
≥once a week	4.47 (3.43 to 5.87)	244	4.42 (3.35 to 5.65)	150	4.71 (3.70 to 6.36)	78	4.70 (3.35 to 5.65)	16

ALDH2, aldehyde dehydrogenase-2; BMI, body mass index; IQR, interquartile range; T-Ad, serum total adiponectin.
*$p < 0.001$, **$p < 0.01$ vs. BMI < 22.0. ***$p < 0.05$ vs. Never or Former.
Data are median (IQR) of serum adiponectin levels. ANOVA with Dunnett's correction was used for BMI or alcohol consumption.

Table 3. Relationship Between Confounding Factors and T-Ad Among the *ADH1B* Genotypes

	All (n = 541)		*ADH1B*					
			*1/*1 (n = 29)		*1/*2 (n = 200)		*2/*2 (n = 312)	
	Median (IQR)	n	Median (IQR)	n	Median (IQR)	n	Median (IQR)	n
Age (years)								
<50	4.49 (3.27 to 5.95)	178	5.25 (3.79 to 6.25)	15	4.58 (3.50 to 5.60)	60	4.24 (3.12 to 6.19)	103
≥50	4.51 (3.44 to 5.91)	363	4.76 (3.86 to 5.23)	14	4.40 (3.33 to 5.94)	140	4.54 (3.46 to 5.92)	209
BMI (kg/m^2)								
<22.0	5.23 (3.68 to 6.94)	163	5.23 (4.16 to 6.33)	9	5.05 (3.59 to 7.04)	61	5.33 (3.79 to 7.04)	93
22.0 to 25.0	4.41* (3.37 to 5.59)	227	5.21 (4.23 to 6.25)	11	4.40*** (3.34 to 5.59)	91	4.31** (3.38 to 5.52)	125
≥25.0	3.92* (3.09 to 5.13)	151	4.39 (3.20 to 5.10)	9	4.34** (3.12 to 5.07)	48	3.79* (3.07 to 5.31)	94
Alcohol consumption (unit a week)								
0 to 4	4.45 (3.38 to 5.94)	186	4.71 (3.70 to 5.01)	7	4.54 (3.19 to 5.62)	63	4.34 (3.33 to 6.26)	116
5 to 11	4.83 (3.60 to 6.10)	178	5.22 (4.11 to 5.86)	10	4.30 (3.36 to 5.73)	62	5.00 (3.59 to 6.22)	106
≥12	4.36 (3.19 to 5.53)	177	4.84 (4.01 to 6.85)	12	4.51 (3.37 to 5.94)	75	3.96**** (3.07 to 5.45)	90
Smoking habit								
Never or Former	4.77 (3.49 to 6.06)	294	5.01 (4.27 to 5.91)	16	4.56 (3.53 to 6.14)	109	4.84 (3.46 to 6.05)	169
Current	4.20† (3.23 to 5.49)	247	4.42 (3.71 to 6.21)	13	4.14 (3.24 to 5.54)	91	4.21 (3.18 to 5.41)	143
Physical exercise								
<once a week	4.51 (3.26 to 5.93)	297	4.63 (3.71 to 5.61)	17	4.55 (3.43 to 5.67)	114	4.41 (3.22 to 6.15)	166
≥once a week	4.47 (3.43 to 5.87)	244	4.91 (4.39 to 6.18)	12	4.34 (3.34 to 6.01)	86	4.52 (3.42 to 5.80)	146

ADH1B, alcohol dehydrogenase-1B; BMI, body mass index; IQR, interquartile range; T-Ad, serum total adiponectin.
*$p < 0.001$, **$p < 0.01$, ***$p < 0.05$ vs. BMI < 22.0. ****$p = 0.052$ vs. 0 to 4 units a week. †$p < 0.05$ vs. Never or Former.
Data are median (IQR) of serum adiponectin levels. ANOVA with Dunnett's correction was used for BMI or alcohol consumption.

*ADH1B*2/*2* genotype, although the association did not reach statistical significance ($p = 0.052$). Significant negative associations with T-Ad levels were observed for BMI and smoking habits among all subjects. BMI was negatively associated with T-Ad levels in those with *ALDH2*1/*1*, *ALDH2*1/*2*, *ADH1B*1/*2*, and *ADH1B*2/*2*.

To assess the relationship of alcohol consumption levels and T-Ad, HMW-Ad, MMW-Ad, or LMW-Ad levels, we performed univariate and multivariate regression analyses of log-transformed values, as shown in Tables 4–7.

Among all subjects, high alcohol consumption of 12 units a week or more was negatively associated with T-Ad levels in the multivariate model, although not significant. High alcohol consumption was negatively associated with LMW-Ad levels in the univariate and multivariate models ($p < 0.05$).

In those with *ADH1B*2/*2*, high alcohol consumption was negatively associated with T-Ad, HMW-Ad, or LMW-Ad levels, but not with MMW-Ad levels, in the univariate and multivariate models ($p < 0.05$).

Table 4. Relationship of Alcohol Consumption Levels and T-Ad Assessed by Regression Analyses Among the Different *ALDH2* and *ADH1B* Genotypes

Alcohol consumption (unit a week)	n	Univariate			Multivariate[a]		
		5 to 11	≥12	p for trend	5 to 11	≥12	p for trend
All	541	1.04 (0.95 to 1.14)	0.95 (0.87 to 1.04)	0.253	1.02 (0.94 to 1.11)	0.94 (0.86 to 1.02)	0.135
ALDH2							
*1/*1	299	1.01 (0.87 to 1.17)	0.95 (0.82 to 1.09)	0.269	1.00 (0.87 to 1.16)	0.92 (0.80 to 1.07)	0.135
*1/*2	191	1.10 (0.96 to 1.26)	0.94 (0.79 to 1.11)	0.849	1.05 (0.92 to 1.20)	0.93 (0.79 to 1.10)	0.628
*2/*2	51	1.37 (0.72 to 2.64)	1.26 (0.66 to 2.42)	0.297	1.21 (0.61 to 2.40)	1.35 (0.69 to 2.64)	0.284
ADH1B							
*1/*1	29	1.14 (0.83 to 1.57)	1.16 (0.85 to 1.58)	0.359	1.11 (0.77 to 1.61)	1.20 (0.86 to 1.68)	0.26
*1/*2	200	1.00 (0.86 to 1.16)	1.02 (0.89 to 1.18)	0.722	0.98 (0.85 to 1.13)	0.98 (0.86 to 1.12)	0.779
*2/*2	312	1.06 (0.95 to 1.19)	0.87* (0.78 to 0.99)	0.044	1.03 (0.92 to 1.16)	0.87* (0.77 to 0.97)	0.025

ADH1B, alcohol dehydrogenase-1B; *ALDH2*, aldehyde dehydrogenase-2; T-Ad, serum total adiponectin.
[a]Adjusted for age, body mass index, smoking, and physical exercise.
*$p < 0.05$.
Logarithmic values were used for analyses. Effect (95% confidence interval) is ratio in average value with reference category (0 to 4 units a week).

Table 5. Relationship of Alcohol Consumption Levels and HMW-Ad Assessed by Regression Analyses Among the Different *ALDH2* and *ADH1B* Genotypes

Alcohol consumption (unit a week)	n	Univariate			Multivariate[a]		
		5 to 11	≥12	p for trend	5 to 11	≥12	p for trend
All	541	1.07 (0.92 to 1.24)	0.92 (0.79 to 1.06)	0.254	1.04 (0.90 to 1.20)	0.89 (0.77 to 1.04)	0.145
ALDH2							
*1/*1	299	0.99 (0.77 to 1.28)	0.90 (0.70 to 1.15)	0.258	0.98 (0.76 to 1.26)	0.87 (0.68 to 1.11)	0.157
*1/*2	191	1.18 (0.93 to 1.50)	0.86 (0.64 to 1.16)	0.702	1.12 (0.88 to 1.42)	0.84 (0.63 to 1.14)	0.534
*2/*2	51	1.57 (0.56 to 4.38)	1.88 (0.67 to 5.22)	0.145	1.31 (0.44 to 3.86)	2.07 (0.72 to 6.03)	0.146
ADH1B							
*1/*1	29	1.17 (0.66 to 2.09)	1.30 (0.75 to 2.27)	0.33	1.14 (0.57 to 2.30)	1.34 (0.71 to 2.51)	0.333
*1/*2	200	1.02 (0.79 to 1.31)	1.03 (0.81 to 1.31)	0.824	0.98 (0.77 to 1.26)	0.94 (0.74 to 1.20)	0.627
*2/*2	312	1.09 (0.90 to 1.33)	0.80* (0.66 to 0.99)	0.056	1.05 (0.86 to 1.28)	0.79* (0.65 to 0.98)	0.04

ADH1B, alcohol dehydrogenase-1B; *ALDH2*, aldehyde dehydrogenase-2; HMW-Ad, serum high-molecular-weight adiponectin.
[a]Adjusted for age, body mass index, smoking, and physical exercise.
*$p < 0.05$.
Logarithmic values were used for analyses. Effect (95% confidence interval) is ratio in average value with reference category (0 to 4 units a week).

Table 6. Relationship of Alcohol Consumption Levels and MMW-Ad Assessed by Regression Analyses Among the Different *ALDH2* and *ADH1B* Genotypes

Alcohol consumption (unit a week)	n	Univariate			Multivariate[a]		
		5 to 11	≥12	p for trend	5 to 11	≥12	p for trend
All	541	1.08 (0.99 to 1.19)	1.05 (0.95 to 1.15)	0.313	1.07 (0.97 to 1.17)	1.03 (0.94 to 1.14)	0.467
ALDH2							
*1/*1	299	1.05 (0.89 to 1.23)	1.04 (0.89 to 1.22)	0.686	1.03 (0.88 to 1.22)	1.02 (0.86 to 1.19)	0.982
*1/*2	191	1.18* (1.02 to 1.36)	1.07 (0.89 to 1.28)	0.183	1.15 (0.99 to 1.32)	1.05 (0.87 to 1.26)	0.291
*2/*2	51	1.07 (0.54 to 2.11)	1.37 (0.69 to 2.71)	0.363	0.93 (0.46 to 1.88)	1.47 (0.74 to 2.94)	0.354
ADH1B							
*1/*1	29	1.24 (0.80 to 1.93)	1.44 (0.94 to 2.20)	0.089	1.21 (0.73 to 2.00)	1.58* (1.01 to 2.48)	0.04
*1/*2	200	1.05 (0.89 to 1.23)	1.15 (0.98 to 1.34)	0.078	1.04 (0.89 to 1.22)	1.12 (0.96 to 1.31)	0.154
*2/*2	312	1.10 (0.97 to 1.24)	0.94 (0.83 to 1.07)	0.46	1.07 (0.95 to 1.21)	0.93 (0.82 to 1.06)	0.334

ADH1B, alcohol dehydrogenase-1B; *ALDH2*, aldehyde dehydrogenase-2; MMW-Ad, serum medium-molecular-weight adiponectin.
[a]Adjusted for age, body mass index, smoking, and physical exercise.
*$p < 0.05$.
Logarithmic values were used for analyses. Effect (95% confidence interval) is ratio in average value with reference category (0 to 4 units a week).

In those with *ALDH2*1/*2,* intermediate alcohol consumption of 5 to 11 units a week was positively associated with MMW-Ad levels only in the univariate model ($p < 0.05$). In those with *ADH1B*1/*1,* high alcohol consumption was positively associated with MMW-Ad levels in the multivariate model ($p < 0.05$).

Table 7. Relationship of Alcohol Consumption Levels and LMW-Ad Assessed by Regression Analyses Among the Different *ALDH2* and *ADH1B* Genotypes

Alcohol consumption (unit a week)	*n*	Univariate			Multivariate[a]		
		5 to 11	≥12	*p* for trend	5 to 11	≥12	*p* for trend
All	541	0.98 (0.91 to 1.06)	0.92* (0.85 to 0.99)	0.034	0.96 (0.90 to 1.04)	0.91* (0.85 to 0.98)	0.015
ALDH2							
**1/*1*	299	0.98 (0.86 to 1.12)	0.93 (0.82 to 1.06)	0.214	0.97 (0.85 to 1.11)	0.91 (0.80 to 1.04)	0.108
**1/*2*	191	0.99 (0.89 to 1.11)	0.92 (0.80 to 1.06)	0.295	0.94 (0.85 to 1.05)	0.92 (0.80 to 1.05)	0.166
**2/*2*	51	1.41 (0.83 to 2.39)	0.68 (0.40 to 1.15)	0.45	1.32 (0.75 to 2.31)	0.70 (0.40 to 1.22)	0.487
ADH1B							
**1/*1*	29	1.07 (0.77 to 1.50)	0.91 (0.66 to 1.25)	0.439	1.03 (0.71 to 1.49)	0.95 (0.69 to 1.33)	0.733
**1/*2*	200	0.95 (0.84 to 1.07)	0.97 (0.86 to 1.09)	0.637	0.93 (0.83 to 1.05)	0.94 (0.84 to 1.06)	0.324
**2/*2*	312	0.99 (0.90 to 1.10)	0.89* (0.80 to 0.98)	0.03	0.97 (0.88 to 1.07)	0.88* (0.79 to 0.98)	0.021

ADH1B, alcohol dehydrogenase-1B; *ALDH2*, aldehyde dehydrogenase-2; LMW, serum low-molecular-weight adiponectin.
[a]Adjusted for age, body mass index, smoking, and physical exercise.
*$p < 0.05$.
Logarithmic values were used for analyses. Effect (95% confidence interval) is ratio in average value with reference category (0 to 4 units a week).

Finally, we evaluated relationships of alcohol intake and T-Ad levels among the different *ALDH2* and *ADH1B* genotype combinations, as shown in Table 8. No significant associations between the 2 different alcohol consumption groups and T-Ad levels were found in all genotype combinations.

DISCUSSION

In the present study, high alcohol consumption of 12 units a week or more was inversely associated with T-Ad levels in all subjects, although the association did not reach statistical significance. Furthermore, high alcohol consumption was negatively associated with T-Ad, HMW-Ad, or LMW-Ad levels in those with *ADH1B*2/*2,* but not in those with the other *ADH1B* genotypes. On the other hand, alcohol intake was not associated with serum adiponectin levels in all of the 3 *ALDH2* genotypes.

Several previous studies have shown that moderate alcohol intake is associated with elevated T-Ad levels in male participants of the Health Professionals Follow-Up Study (Pischon et al., 2005), in Japanese women (Kotani et al., 2007), and in Japanese men with MetS (Makita et al., 2013). In contrast, other recent studies have shown that alcohol intake and T-Ad levels (Nishise et al., 2010) or HMW-Ad levels (Kawamoto et al., 2010) are inversely associated in Japanese men. One recent study has shown that heavy alcohol drinking (90 g a day or more) is related to lower T-Ad levels in Korean men (Jung et al., 2013). In the present study, high alcohol consumption had a tendency to be inversely associated with T-Ad levels in all subjects, in accordance with the recent studies. Several experimental studies have also shown that chronic EtOH treatment results in decreases in circulating adiponectin levels in both rats (Chen et al., 2009) and mice (Xu et al., 2003).

In the present study, a negative association of high alcohol consumption and T-Ad levels was observed particularly in those with *ADH1B*2/*2.* Those with this genotype have higher ADH activity (Yin et al., 1984) and may produce higher acetaldehyde levels in various organs. Therefore, acetaldehyde accumulated in adipose tissue by habitual alcohol drinking may inhibit a secretion of adiponectin particularly in those with this genotype. Acetaldehyde has been shown to induce inflammatory markers, such as TNF-α or other cytokines in HepG2 cells (Hsiang et al., 2005). TNF-α or other pro-inflammatory cytokines have been reported to suppress secretion of adiponectin (Fasshauer et al., 2003; Maeda

Table 8. Relationship of Alcohol Consumption Levels and T-Ad Assessed by Regression Analyses Among the Different *ALDH2* and *ADH1B* Genotype Combinations

Alcohol consumption (unit a week)		*n*	Univariate			Multivariate[a]		
			5 to 11	≥12	*p* for trend	5 to 11	≥12	*p* for trend
All		541	1.04 (0.95 to 1.14)	0.95 (0.87 to 1.04)	0.253	1.02 (0.94 to 1.11)	0.94 (0.86 to 1.02)	0.135
ALDH2	*ADH1B*							
**1/*1*	**1/*1 + *1/*2*	131	0.86 (0.69 to 1.07)	0.92 (0.75 to 1.13)	0.681	0.87 (0.70 to 1.07)	0.90 (0.73 to 1.10)	0.478
**1/*1*	**2/*2*	168	1.15 (0.94 to 1.41)	0.98 (0.80 to 1.19)	0.248	1.12 (0.91 to 1.37)	0.94 (0.77 to 1.16)	0.126
**1/*2*	**1/*1 + *1/*2*	77	1.20 (0.99 to 1.45)	1.14 (0.92 to 1.41)	0.161	1.14 (0.93 to 1.39)	1.09 (0.87 to 1.37)	0.345
**1/*2*	**2/*2*	114	1.06 (0.88 to 1.28)	0.78 (0.60 to 1.02)	0.242	1.01 (0.84 to 1.22)	0.82 (0.63 to 1.08)	0.306

ADH1B, alcohol dehydrogenase-1B; *ALDH2*, aldehyde dehydrogenase-2; T-Ad, serum total adiponectin.
[a]Adjusted for age, body mass index, smoking, and physical exercise.
Logarithmic values were used for analyses. Effect (95% confidence interval) is ratio in average value with reference category (0 to 4 units a week).

et al., 2001; Wang et al., 2005). Alternatively, elevated acetaldehyde levels may cause oxidative stress, which would decrease expression of adiponectin gene (Hattori et al., 2005). The observed negative association among those with *ADH1B*2/*2* might partly explain why the negative association has been reported only in Asian countries. Further studies with larger sample size are necessary to confirm the present finding.

Plasma adiponectin levels are low in people who have type 2 diabetes (Matsuzawa et al., 2011). One recent study has shown that the presence of the *ADH1B*2* allele was associated with significantly increased age-adjusted odds ratios for diabetes mellitus among Japanese alcoholic men (Yokoyama et al., 2013), which could be in line with the present results.

We measured levels of the 3 different forms of serum adiponectin; HMW-Ad, MMW-Ad, and LMW-Ad, in addition to T-Ad levels. Among all subjects, high alcohol consumption was negatively associated with LMW-Ad levels, but not with the other forms. In those with *ADH1B*2/*2*, high alcohol consumption was negatively associated with HMW-Ad and LMW-Ad levels, which result is in good accordance with the results for T-Ad as discussed above. HMW-Ad is assumed to be an active form of adiponectin (Kobayashi et al., 2004), and HMW-Ad is regarded as a good predictive marker for type 2 diabetes and cardiovascular diseases (Heidemann et al., 2008; Pischon et al., 2011). However, whether HMW-Ad can predict health risks better than T-Ad is still controversial (Heidemann et al., 2008; Pischon et al., 2011). Information on the significance of the other forms is limited at the present time. Further extensive studies are needed to clarify relationships between levels of different forms of adiponectin, alcohol intake, and health effects.

Although the intermediate alcohol consumption group with *ALDH2*1/*2* and the high alcohol consumption group with *ADH1B*1/*1* were positively associated with MMW-Ad levels, we need further studies with a larger number of subjects to confirm these results because these relationships were not significant in the other forms of adiponectin.

We could not observe significant effects of alcohol intake on T-Ad levels in all genotype combinations. More extensive studies with a larger number of subjects are required to clarify the relationship for each genotype combination.

The present study has several limitations. First, the cross-sectional study design does not provide a causal inference regarding the association between alcohol intake and serum adiponectin levels. However, it is likely that heavy alcohol consumption in those with the *ADH1B*2/*2* genotype has low serum adiponectin levels, because the habit of alcohol intake likely continues for years. Prospective studies are needed to confirm the causal relationships between alcohol intake and serum adiponectin levels.

Second, the response rate of 32.5% (731/2,247) was not so high. It is likely that the participants have more concern about their own health management than those who did not participate. This selection bias may have influenced the present results to some extent. However, at least there were no significant differences in BMI, proportions of the smokers, the physical activity level, and alcohol consumption between the participants and nonparticipants of 40 years old or more (data not shown).

Third, the present study relied on a self-reported drinking status, which may lead to the possibility of misclassification of exposure (e.g., underreporting). However, it is also unlikely that this type of misclassification is directly dependent on serum adiponectin levels, which could be a nondifferential misclassification.

In conclusion, high alcohol consumption was inversely associated with T-Ad, HMW-Ad, and LMW-Ad levels in those with *ADH1B*2/*2* genotype, but not in those with the other *ADH1B* genotypes. To our knowledge, this is the first study which reports combined effects of the alcohol-related polymorphisms and alcohol intake on serum adiponectin levels. Further investigations in Japanese subjects among the *ALDH2* and *ADH1B* genotypes are necessary to clarify the factors that modulate this inverse effect. Hypoadiponectinemia has been demonstrated to be related to MetS, type 2 diabetes, cardiovascular disease, and several types of cancer (Heidemann et al., 2008; Matsuzawa, 2010; Matsuzawa et al., 2011; Pischon et al., 2004, 2011). We will investigate the effects of both *ALDH2* and *ADH1B* genotypes and alcohol intake on blood pressure, blood glucose, and the other biomarkers related to MetS in follow-up studies with larger sample size.

ACKNOWLEDGMENTS

A Grant-in-Aid for Scientific Research was received from the Ministry of Education, Culture, Sports, Science and Technology, Japan (17590524, 21590658, 25460811, and 25670301).

REFERENCES

Anonymous (2013) Health, Labour and Welfare Statistics Association. Health and Welfare Statistics in Japan. J Health Welfare Statistics 60:97–98.

Aprahamian TR, Sam F (2011) Adiponectin in cardiovascular inflammation and obesity. Int J Inflam doi:10.4061/2011/376909.

Chen CC, Lu RB, Chen YC, Wang MF, Chang YC, Li TK, Yin SJ (1999) Interaction between the functional polymorphisms of the alcohol-metabolism genes in protection against alcoholism. Am J Hum Genet 65:795–807.

Chen X, Sebastian BM, Tang H, McMullen MM, Axhemi A, Jacobsen DW, Nagy LE (2009) Taurine supplementation prevents ethanol-induced decrease in serum adiponectin and reduces hepatic steatosis in rats. Hepatology 49:1554–1562.

Enomoto N, Takase S, Yasuhara M, Takada A (1991) Acetaldehyde metabolism in different aldehyde dehydrogenase-2 genotypes. Alcohol Clin Exp Res 15:141–144.

Fasshauer M, Kralisch S, Klier M, Lossner U, Bluher M, Klein J, Paschke R (2003) Adiponectin gene expression and secretion is inhibited by interleukin-6 in 3T3-L1 adipocytes. Biochem Biophys Res Commun 301:1045–1050.

Ford ES (2005) Prevalence of the metabolic syndrome defined by the International Diabetes Federation among adults in the U.S. Diabetes Care 28:2745–2749.

Gulcelik MA, Colakoglu K, Dincer H, Dogan L, Yenidogan E, Gulcelik NE (2012) Associations between adiponectin and two different cancers: breast and colon. Asian Pac J Cancer Prev 13:395–398.

Hattori Y, Akimoto K, Gross SS, Hattori S, Kasai K (2005) Angiotensin-II-induced oxidative stress elicits hypoadiponectinaemia in rats. Diabetologia 48:1066–1074.

Heidemann C, Sun Q, van Dam RM, Meigs JB, Zhang C, Tworoger SS, Mantzoros CS, Hu FB (2008) Total and high-molecular-weight adiponectin and resistin in relation to the risk for type 2 diabetes in women. Ann Intern Med 149:307–316.

Higuchi S, Matsushita S, Murayama M, Takagi S, Hayashida M (1995) Alcohol and aldehyde dehydrogenase polymorphisms and the risk for alcoholism. Am J Psychiatry 152:1219–1221.

Hsiang CY, Wu SL, Cheng SE, Ho TY (2005) Acetaldehyde-induced interleukin-1beta and tumor necrosis factor-alpha production is inhibited by berberine through nuclear factor-kappaB signaling pathway in HepG2 cells. J Biomed Sci 12:791–801.

Iso H, Sato S, Kitamura A, Imano H, Kiyama M, Yamagishi K, Cui R, Tanigawa T, Shimamoto T (2007) Metabolic syndrome and the risk of ischemic heart disease and stroke among Japanese men and women. Stroke 38:1744–1751.

Jung SK, Kim MK, Shin J, Choi BY (2013) A cross-sectional analysis of the relationship between daily alcohol consumption and serum adiponectin levels among adults aged 40 years or more in a rural area of Korea. Eur J Clin Nutr 67:841–847.

Kawamoto R, Tabara Y, Kohara K, Miki T, Ohtsuka N, Kusunoki T, Abe M (2010) Alcohol drinking status is associated with serum high molecular weight adiponectin in community-dwelling Japanese men. J Atheroscler Thromb 17:953–962.

Kobayashi H, Ouchi N, Kihara S, Walsh K, Kumada M, Abe Y, Funahashi T, Matsuzawa Y (2004) Selective suppression of endothelial cell apoptosis by the high molecular weight form of adiponectin. Circ Res 94:e27–e31.

Kotani K, Sakane N, Saiga K, Sano Y, Kurozawa Y (2007) Lifestyle-related determinants and serum adiponectin concentrations in a general population of Japanese females. Arch Med Res 38:887–890.

Lieber CS (1995) Medical disorders of alcoholism. N Engl J Med 333:1058–1065.

Macgregor S, Lind PA, Bucholz KK, Hansell NK, Madden PA, Richter MM, Montgomery GW, Martin NG, Heath AC, Whitfield JB (2009) Associations of ADH and ALDH2 gene variation with self report alcohol reactions, consumption and dependence: an integrated analysis. Hum Mol Genet 18:580–593.

Maeda N, Takahashi M, Funahashi T, Kihara S, Nishizawa H, Kishida K, Nagaretani H, Matsuda M, Komuro R, Ouchi N, Kuriyama H, Hotta K, Nakamura T, Shimomura I, Matsuzawa Y (2001) PPARgamma ligands increase expression and plasma concentrations of adiponectin, an adipose-derived protein. Diabetes 50:2094–2099.

Makita S, Abiko A, Nagai M, Yonezawa S, Koshiyama M, Ohta M, Nakamura M (2013) Influence of daily alcohol consumption on serum adiponectin levels in men. Metabolism 62:411–416.

Matsuse H, Shimoda T, Fukushima C, Mitsuta K, Kawano T, Tomari S, Saeki S, Kondoh Y, Machida I, Obase Y, Asai S, Kohno S (2001) Screening for acetaldehyde dehydrogenase 2 genotype in alcohol-induced asthma by using the ethanol patch test. J Allergy Clin Immunol 108:715–719.

Matsuzawa Y (2010) Establishment of a concept of visceral fat syndrome and discovery of adiponectin. Proc Jpn Acad Ser B Phys Biol Sci 86:131–141.

Matsuzawa Y, Funahashi T, Nakamura T (2011) The concept of metabolic syndrome: contribution of visceral fat accumulation and its molecular mechanism. J Atheroscler Thromb 18:629–639.

Nishise Y, Saito T, Makino N, Okumoto K, Ito JI, Watanabe H, Saito K, Togashi H, Ikeda C, Kubota I, Daimon M, Kato T, Fukao A, Kawata S (2010) Relationship between alcohol consumption and serum adiponectin levels: the Takahata study—a cross-sectional study of a healthy Japanese population. J Clin Endocrinol Metab 95:3828–3835.

Pischon T, Girman CJ, Hotamisligil GS, Rifai N, Hu FB, Rimm EB (2004) Plasma adiponectin levels and risk of myocardial infarction in men. JAMA 291:1730–1737.

Pischon T, Girman CJ, Rifai N, Hotamisligil GS, Rimm EB (2005) Association between dietary factors and plasma adiponectin concentrations in men. Am J Clin Nutr 81:780–786.

Pischon T, Hu FB, Girman CJ, Rifai N, Manson JE, Rexrode KM, Rimm EB (2011) Plasma total and high molecular weight adiponectin levels and risk of coronary heart disease in women. Atherosclerosis 219:322–329.

Takeshita T, Mao XQ, Morimoto K (1996) The contribution of polymorphism in the alcohol dehydrogenase beta subunit to alcohol sensitivity in a Japanese population. Hum Genet 97:409–413.

Takeshita T, Morimoto K, Mao X, Hashimoto T, Furuyama J (1994) Characterization of the three genotypes of low Km aldehyde dehydrogenase in a Japanese population. Hum Genet 94:217–223.

Takeshita T, Yang X, Morimoto K (2001) Association of the ADH2 genotypes with skin responses after ethanol exposure in Japanese male university students. Alcohol Clin Exp Res 25:1264–1269.

Tsuchihashi-Makaya M, Serizawa M, Yanai K, Katsuya T, Takeuchi F, Fujioka A, Yamori Y, Ogihara T, Kato N (2009) Gene-environmental interaction regarding alcohol-metabolizing enzymes in the Japanese general population. Hypertens Res 32:207–213.

Wang B, Jenkins JR, Trayhurn P (2005) Expression and secretion of inflammation-related adipokines by human adipocytes differentiated in culture: integrated response to TNF-alpha. Am J Physiol Endocrinol Metab 288: E731–E740.

Xu A, Wang Y, Keshaw H, Xu LY, Lam KS, Cooper GJ (2003) The fat-derived hormone adiponectin alleviates alcoholic and nonalcoholic fatty liver diseases in mice. J Clin Invest 112:91–100.

Yang SJ, Yokoyama A, Yokoyama T, Huang YC, Wu SY, Shao Y, Niu J, Wang J, Liu Y, Zhou XQ, Yang CX (2010) Relationship between genetic polymorphisms of ALDH2 and ADH1B and esophageal cancer risk: a meta-analysis. World J Gastroenterol 16:4210–4220.

Yin SJ, Bosron WF, Magnes LJ, Li TK (1984) Human liver alcohol dehydrogenase: purification and kinetic characterization of the beta 2 beta 2, beta 2 beta 1, alpha beta 2, and beta 2 gamma 1 "Oriental" isoenzymes. Biochemistry 23:5847–5853.

Yokoyama A, Mizukami T, Matsui T, Yokoyama T, Kimura M, Matsushita S, Higuchi S, Maruyama K (2013) Genetic polymorphisms of alcohol dehydrogenase-1B and aldehyde dehydrogenase-2 and liver cirrhosis, chronic calcific pancreatitis, diabetes mellitus, and hypertension among Japanese alcoholic men. Alcohol Clin Exp Res 37:1391–1401.

Yokoyama A, Muramatsu T, Ohmori T, Higuchi S, Hayashida M, Ishii H (1996) Esophageal cancer and aldehyde dehydrogenase-2 genotypes in Japanese males. Cancer Epidemiol Biomarkers Prev 5:99–102.

Yokoyama A, Watanabe H, Fukuda H, Haneda T, Kato H, Yokoyama T, Muramatsu T, Igaki H, Tachimori Y (2002) Multiple cancers associated with esophageal and oropharyngolaryngeal squamous cell carcinoma and the aldehyde dehydrogenase-2 genotype in male Japanese drinkers. Cancer Epidemiol Biomarkers Prev 11:895–900.

Environ Health Prev Med (2014) 19:444–451
DOI 10.1007/s12199-014-0404-8

SHORT COMMUNICATION

Safety and adherence of *Umezu* polyphenols in the Japanese plum (*Prunus mume*) in a 12-week double-blind randomized placebo-controlled pilot trial to evaluate antihypertensive effects

Shigeki Takemura · Kouichi Yoshimasu · Jin Fukumoto · Kanae Mure · Nobuhiro Nishio · Kunihiro Kishida · Fumiko Yano · Takahiko Mitani · Tatsuya Takeshita · Kazuhisa Miyashita

Received: 24 April 2014 / Accepted: 11 August 2014 / Published online: 13 September 2014
© The Japanese Society for Hygiene 2014

Abstract

Objectives Medications or lifestyle changes to prevent or improve hypertension often press considerable efforts on patients suffering from mild hypertension. Capsules including *Umezu* polyphenols (UP), polyphenols in Japanese plums, may help them to control their blood pressure (BP). The aim of this study is to evaluate the effectiveness of UP on BP and its safety.

Methods A total of 15 healthy workers without antihypertensive medication who had some concerns about their BP, preferably normal-high BP or hypertension level 1, were randomized in a double-blind manner into UP ingesting and placebo groups. Each subject was instructed to take four capsules daily for 12 weeks (daily UP dose, 800 mg for the UP ingesting group; and 0 mg for the placebo group). These subjects were followed for 12 weeks, and their BP both at home and at the examination site, as well as self-perceived quality-of-life outcomes and possible side effects, was monitored during that period. Group × time interactions on BP changes were examined.

Results All of the 15 subjects completed the 12-week intervention trial. The BP changes did not significantly differ between the UP ingesting and placebo groups, neither at the examination site nor at home. But during the study period, no adverse effects were observed.

Conclusions No remarkable effect of UP on BP was observed. However, a higher dose of UP was confirmed safe and high in adherence in this 12-week randomized controlled trial. Its effect on BP and other outcomes shall be confirmed in a larger sample.

Keywords Hypertension · Prevention · Japanese plum · Polyphenol · Randomized placebo-controlled trial

A part of this study was presented in the 72nd Annual Meeting of the Japanese Society of Public Health on October 23–25, 2013.

S. Takemura (✉) · K. Yoshimasu · J. Fukumoto · K. Miyashita
Department of Hygiene, School of Medicine, Wakayama Medical University, 811-1 Kimiidera, Wakayama 641-8509, Japan
e-mail: steakmmi@hotmail.com

K. Mure · N. Nishio · T. Takeshita
Department of Public Health, School of Medicine, Wakayama Medical University, Wakayama, Japan

K. Kishida · F. Yano · T. Mitani
Biology-Oriented Science and Technology, Kinki University, Wakayama, Japan

T. Mitani
Wakayama Industry Promotion Foundation, Wakayama, Japan

Introduction

Hypertension is one of the major risk factors associated with cardio- and cerebrovascular diseases, and has a strong impact on global health. In Japan, the mortality rates from those diseases have declined since the second half of 1960s, which is considered to be partially due to the decline in blood pressure (BP) levels and the lower prevalence of hypertension during the years 1965–1990 [1]. However, it is estimated that there are still 40 million people with hypertension in Japan [2]. It is a serious concern that many of those with hypertension do not receive appropriate treatments for hypertension, especially among young and middle-aged people. When hypertension is defined as 140 mmHg or more of systolic blood pressure (SBP) and/or 90 mmHg or more of diastolic blood pressure (DBP), about 80–90 % of Japanese in their thirties and forties with hypertension are considered not to have

received any treatment [2]. Since most of the existing antihypertensive drugs often show some adverse effects, their applications are limited, especially for those with mild hypertension who are approaching clinically dangerous levels. Therefore, those people should lower their BPs, at least by changing their lifestyles to healthier ones. Although low-salt diets and exercise are proven to be effective against hypertension, following through with them is often burdensome for those people. Regarding dietary factors, high consumption of fruits and vegetables has been correlated with a decrease in cardiovascular disease [3–5]. However, intake of fruits and vegetables cannot be strongly recommended for patients with serious renal failure, since such diets may induce hyperkalemia in them [2]. Furthermore, excessive intake of fruits with high concentrations of glucose should be avoided by people with diabetes mellitus.

On the other hand, significant protective effects of antioxidants included in vegetables and fruits have been noted [6], while interventional trials of antioxidants have provided mixed results, some showing deleterious ones [6, 7]. Among those antioxidants, polyphenols from tea, wine, grapes, berries and other plants have been shown to activate endothelial cells and to increase the formation of potent vasoprotective factors, including nitric oxide (NO) and endothelium-derived hyperpolarizing factors. In addition, polyphenols interfere with mechanisms that lead to inflammation, platelet aggregation, and endothelial apoptosis, and contribute to the prevention of endothelial dysfunction, which is known to play a central role in the pathogenesis of cardiovascular diseases [8–11].

Polyphenols are found abundantly in fruits such as plums or prunes. Interestingly, the prune was reported to have protective effects against cardiovascular diseases, inducing significant reductions of BP and reducing serum cholesterol and LDL [12]. This effect was considered to be due to the antioxidant constituents of prunes [12]. If such constituents were added to common soft drinks, people with mild hypertension might successfully reduce their BP without having to make considerable efforts. In this regard, Japanese plums, especially the well-known products of Wakayama Prefecture in Japan, have been reported to be effective for improving human health including cardiovascular conditions [13, 14].

Based on the above-mentioned background, we performed a double-blind randomized study in 2011, using *Umezu* polyphenols (UP), i.e., polyphenols extracted from Japanese plums (Japanese name, *Ume*; botanical name, *Prunus mume*), which unsuccessfully revealed BP-lowering effects [15]. This may be due to some factors including a relatively short study period (5 weeks) and insufficiency of the dose (200 mg of UP daily). Then, we conducted a 12-week RCT, with a higher dose of UP.

Materials and methods

Subjects

We conducted a preliminary study using a sample of workers (clerical workers, university faculty members, physicians and comedicals) in our principal study center from December 2012 to March 2013. We recruited study participants interested in prevention or control of their hypertension, especially from those with normal-high BP (SBP, 130–139 mmHg; or DBP, 85–89 mmHg) or hypertension grade 1 (SBP, 140–159 mmHg; or DBP, 90–99 mmHg) taking no antihypertensive agents [2]. Those who met the following exclusive criteria could not participate in the study: (1) those who ate 2 or more *Umeboshi* (pickled plums) per day, (2) those under medication for hypertension, (3) those with serious somatic disorders including cerebrovascular disease, ischemic heart disease, cancer, and diabetes mellitus, (4) those who were pregnant or within 1 year after delivery, (5) those with ingestion difficulty, (6) those having night-shift work with night duty, and (7) those who could not participate in the periodical physical measurement.

A total of 15 workers [13 men and 2 women; mean (SD) of age, 43.2 (12.4) years] participated in the study. They were randomly divided into 2 groups [Group A (n = 8) and Group B (n = 7)] whose sex and age distributions were adjusted to be as equal as possible (Fig. 1). Group A received placebo capsules (0 mg of UP per capsule), while Group B received capsules containing UP (200 mg of UP

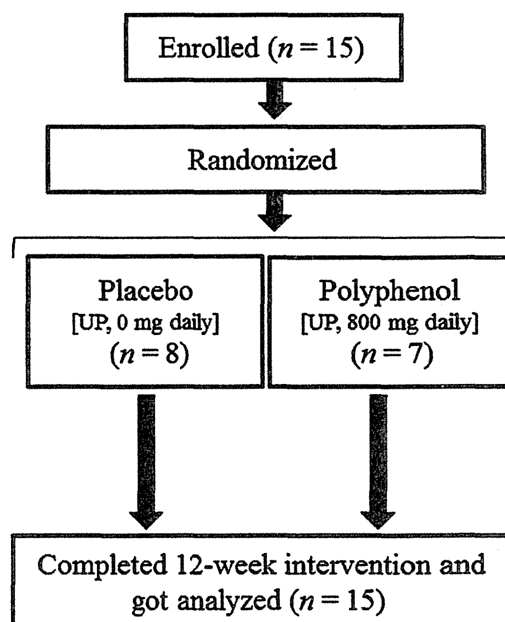

Fig. 1 *Flowchart* of subject enrollment, intervention and analysis. UP, *Umezu* polyphenols

per capsule). They were instructed to take four capsules daily for 12 weeks, and the total daily dosage of UP was 0 and 800 mg in Group A and Group B, respectively. These dosages were determined based on the study results of rats conducted in advance (data not shown). The study period of 12 weeks was determined, pursuant to the principle the Consumer Affairs Agency, Government of Japan (formerly the Ministry of Health, Labor and Welfare, Government of Japan) shows. The Agency generally requires an intervention trial of 12 weeks or longer to approve *Tokuho*, or foods for specified health uses (e.g., BP lowering) [16].

The mean (SD) of age among the 15 participants was 43.2 (12.4) years. When the study began, at the examination site, 1 of the 15 was at hypertension grade 2 (SBP, 160–179 mmHg, or DBP, 100–109 mmHg) (who was at hypertension 1 in subsequent measurements), 6 at hypertension grade 1, and 3 at normal-high BP at the examination site; at home, 6 were at hypertension grade 1 and 3 at normal-high BP.

Neither the examiners nor subjects knew which kind of capsules were being taken (i.e., double-blind design) throughout the study period. The current study was approved by the Institutional Review Board of Wakayama Medical University. Informed consent was acquired from all the participants in written form.

Extraction of polyphenols

Fruit samples of *Prunus mume* cv. 'Nanko' were randomly collected from one fixed tree grown at the experimental orchard of the Laboratory of Japanese Plum, Fruit Tree Experiment Station, Wakayama Research Center of Agriculture, Minabe Town, from 2006 to 2008, and stored in polyethylene bags at −20 °C until analysis.

Since details surrounding the determination of total polyphenols and the preparation of polyphenol fractions through a biochemical experimental system are beyond the current study's scope, they will be described elsewhere [17, 18]. In brief, the Folin–Ciocalteu method with gallic acid as a standard was used for the determination of total polyphenols, and a batch method was adopted for the preparation of polyphenol fractions.

Umezu polyphenols were found to show many chromatographically isolated peaks. Our experimental analysis clarified that the UP were chemically composed of hydroxycinnamic acid derivatives. Four aglycones were identified as *cis-p*-coumaric acid, *trans-p*-coumaric acid, caffeic acid, and ferulic acid. Those aglycones are bound to various kinds of organic acids or sugars, and exist as the ingredients of UP. The extracted UP were sent to a supplement manufacturer (Kyoto Nourishment Natural Chemical Laboratory Co., Ltd., Kyoto, Japan), and added into supplement capsules.

Blood pressure, and physical and mental conditions

Study subjects were asked to measure their SBP and DBP early in the morning (after urinating and/or defecating, and before eating breakfast) and before sleep at night every day (it was not restricted for subjects to consume alcoholic beverages or take a bath before measuring the night BP measurement); SBP and DBP of the right arm were measured with an automatic sphygmomanometer (HEM-747IC, Omron, Tokyo, Japan), twice in a sitting position with arms supported at the right atrium level. When the difference of SBP between the first measure and the second measure was 10 mmHg or greater, BP was measured one more time (a total of three times). At the beginning of the study, the principal investigator (ST) individually instructed each study subject how to measure BP and record it in the paper-based journal at home.

Blood pressure was measured at the examination site in the morning (8:30 a.m. to 0:00 p.m.) at baseline and 1, 2, 4, 6, 8, 10 and 12 weeks later. At the examination site, SBP and DBP were measured with an automatic sphygmomanometer (HEM-907, Omron, Tokyo, Japan) by research staff (a trained physician or nurse), twice in a sitting position with arms supported at the right atrium level. When the difference of SBP between the first measure and the second measure was 10 mmHg or greater, BP was measured one more time (a total of three times).

To evaluate changes in subjective health conditions, subjects' perceived physical and mental quality of life (QOL) was assessed at baseline and 4, 8 and 12 weeks later by SF-8 [19]. A higher SF-8 score [physical component summary (PCS) or mental component summary (MCS)] indicates a better physical/mental condition. In Japanese people, the average score and the standard deviation are 50 points and 10 points, respectively.

To ensure the safety of subjects, they were asked about their conditions including signs and symptoms at each of their visits of the examination site. When they reported some signs and symptoms, they were further asked if these signs and symptoms manifested themselves after taking UP or placebo capsules.

Statistical analysis

We calculated the mean value of subject-measured BP for each day, including all measured values, then we defined the BP at the beginning of the study (week 0) as the mean value of the BP measured on the first day of the measurement, and the BP at each week (weeks 1–12) as the mean value of all 7 days of the week, excluding the data for week 0. We also calculated the mean value of staff-measured BP, for each follow-up session (weeks 1, 2, 4, 6, 8, 10 and 12, if available) as well as the beginning of the study period (week 0). These BP values were chosen as outcome variables. As for SF-8, PCS and MCS were outcome variables.

Table 1 Characteristics of study subjects at baseline

	Placebo group ($n = 8$)	Polyphenol group ($n = 7$)	p^a
Daily dose of *Umezu* polyphenols (mg)	0	800	–
Age (years)	42.3 (12.2)	44.3 (13.5)	0.764
Sex: male [n (%)]	7 (87.5)	6 (85.7)	1.000
Height (cm)	169.7 (6.6)	166.7 (8.0)	0.437
Weight (kg)	71.4 (17.0)	69.6 (14.9)	0.835
Body mass index (kg/m^2)	24.5 (4.2)	24.8 (3.4)	0.880
Waist circumference (cm)	89.0 (10.9)	86.4 (13.2)	0.688
Hip circumference (cm)	100.9 (9.0)	98.7 (8.2)	0.637
Waist–hip ratio	0.880 (0.039)	0.873 (0.095)	0.870
BP and pulse			
Examination site			
Systolic BP (mmHg)	133.0 (12.4)	138.5 (16.4)	0.468
Diastolic BP (mmHg)	84.3 (10.9)	89.9 (8.1)	0.281
Pulse (counts/min)	66.3 (4.4)	69.9 (3.4)	0.106
Home in the morning			
Systolic BP (mmHg)	129.5 (13.4)	136.1 (13.3)	0.358
Diastolic BP (mmHg)	84.0 (7.2)	89.4 (11.1)	0.279
Pulse (counts/min)	64.1 (5.4)	68.5 (6.0)	0.158
Home at night			
Systolic BP (mmHg)	126.4 (14.6)	135.2 (17.6)	0.307
Diastolic BP (mmHg)	74.4 (12.8)	86.1 (12.6)	0.099
Pulse (counts/min)	71.9 (12.0)	75.3 (11.4)	0.592

Figures denote average (standard deviation), unless otherwise specified

BP blood pressure

[a] Unpaired t test or Fisher's exact test

To compare the baseline characteristics between the polyphenol group and the placebo group, unpaired t test was conducted for continuous variables, and Fisher's exact test for categorical variables. Two-way analysis of variance (ANOVA) was conducted for comparing the variation of BP, PCS and MCS between/among the groups during the study period. In each group, time-dependent repeated-measure analyses and Dunnett's test were performed [vs. data at baseline (week 0)]. In case Dunnett's test was unavailable, paired t test was conducted instead. p-values (two-sided) less than 0.05 were considered statistically significant. All analyses were conducted using SAS software, version 9.1 (SAS Institute, Inc., Cary, NC, USA).

Results

Baseline characteristics

Shown are the baseline characteristics of study subjects in the polyphenol group and in the placebo group in Table 1.

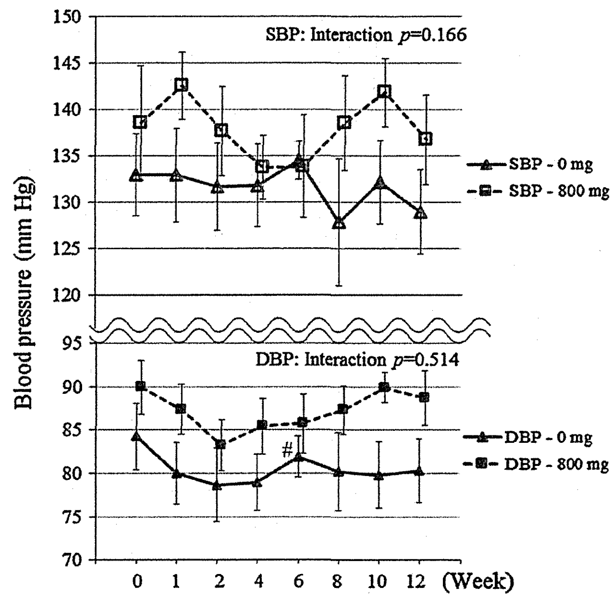

Fig. 2 Effect of *Umezu* polyphenols on blood pressure measured at the examination site. Time-dependent repeated-measure analyses and Dunnett's test were performed (vs. data in week 0). The interaction between intervention and time was also evaluated ($^{\#}p < 0.10$). *SBP* systolic blood pressure, *DBP* diastolic blood pressure

We did not observe significant differences between the two groups, which were partly due to the small number of the study subjects ($n = 15$).

Blood pressure at the examination site

Changes of BP in study subjects measured by research staff at the examination site are presented in Fig. 2. During the study period, the BP fluctuated in both the groups, resulting in a nonsignificant finding in SBP and DBP. The discrepancy of BP between the two groups remained during the study.

Blood pressure at home

Figure 3 shows changes in self-measured BP at home, (a) in the morning, and (b) at night. In the morning BP (Fig. 3a), SBP did not decrease in the polyphenol group, while DBP tended to decrease in both the groups, not reaching significance.

In the night BP (Fig. 3b), SBP and DBP fluctuated to produce some significant to quasi-significant values, although the interaction analysis did not show significant effects of UP on BP.

The discrepancy of BP between the two groups remained during the study.