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How to Reduce the Threat of Colorectal Cancer? From the Viewpoints of Lifestyle-related Diseases to Preventive Medicine

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Abstract

Colorectal cancer (CRC) is an important public health problem. Both hereditary and environmental factors interact to result in sequential occurrence from adenoma to adenocarcinoma. In terms of natural history of CRC development and progression, three strategies are available to improve its outcome. Identification of modifiable risk factors and adopting a healthy diet and lifestyle, named as primary prevention, can decrease the occurrence of CRC. For asymptomatic high-risk population, early detection by screening can greatly increase survival and even reduce the incidence, which is called secondary prevention. In symptomatic patients who are diagnosed as CRC at later stage, tertiary prevention through surgery, chemotherapy, target or immune therapy, aims to prolong survival and improve life quality. Although tertiary prevention is the current standard of clinical practice, the effects of primary and secondary prevention are obviously better than tertiary prevention from preventive medicine viewpoints. In the era of precision medicine, further challenges in CRC prevention and screening program should move beyond one size fits all and embrace more personalized program. My practice in Ningen Dock show integrated approaches to combine primary and secondary prevention is the best way to optimize the efforts for improving CRC prevention and survival.

Keywords colorectal cancer, screening, primary prevention, secondary prevention

Introduction: Colorectal Cancer Has Become the Most Prevalent Malignancy in Taiwan

Colorectal cancer (CRC) ranks the third most common cancer in men and second in women worldwide[1]. With westernization of dietary habit and lifestyle, there is an increasing trend of CRC in Asia. In Taiwan, CRC has become the most prevalent malignancy since 2006. The age-standardized rate (ASR) of CRC incidence is 45 per 10^5 and ASR for mortality is 14.7 per 10^5 [2]. Accordingly, CRC is an important public health problem in Taiwan.

Three Strategies for Improving Colorectal Cancer Outcome

CRC carcinogenesis is a multifactorial and multistep process. Both hereditary and environmental factors interact to result in sequential occurrence from adenoma to adenocarcinoma. In terms of natural history of CRC development and progression, three strategies are available to improve its outcome (**Fig. 1**). Identification of modifiable risk factors and adopting a healthy diet and lifestyle, named as primary prevention, can decrease the occurrence of CRC. For asymptomatic high-risk population, early detection by screening can greatly increase survival and even reduce the incidence, which is called secondary prevention. In symptomatic patients who are diagnosed as CRC at later stage, tertiary prevention through surgery, chemotherapy, target or immune therapy, aims to prolong survival and improve life quality. Although tertiary prevention is the current standard of clinical practice, the effects of primary and secondary prevention are obviously better than tertiary prevention from preventive medicine viewpoints.

Secondary Prevention: Stool or Scope

Secondary prevention is based on screening tests for early detection and then early intervention of adenoma or early stage of adenocarcinoma. CRC screening tests can be classified into two categories: fecal/blood tests that primarily detect cancer, and structural examinations that can detect both adenomatous polyps and cancer[3]. The former identifies at-risk people for cancerous

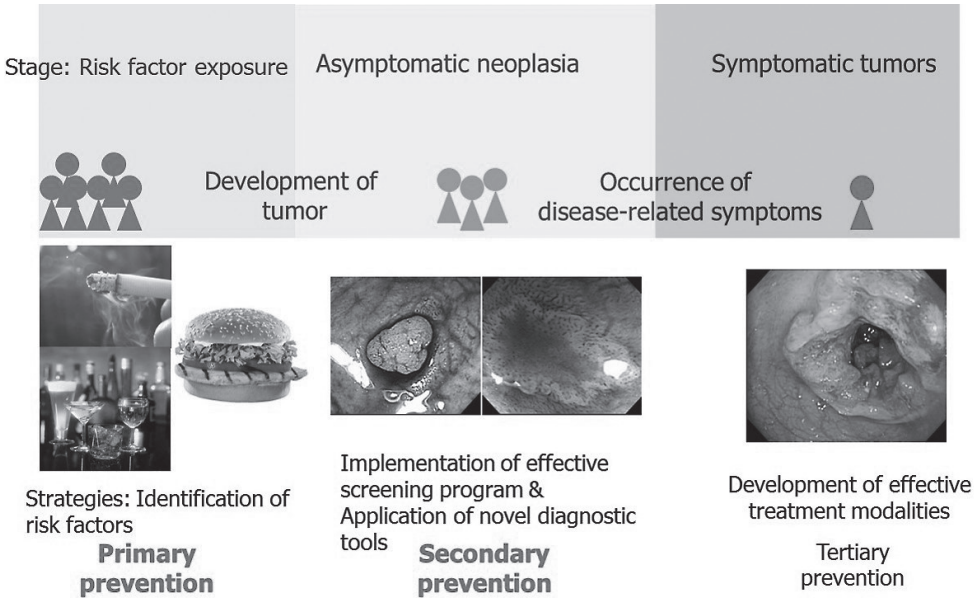

Fig. 1. Strategies for Improving Outcomes of Colon Cancer

lesion and only people with abnormal findings require further definite examinations such as endoscopy. These non-invasive tests include various blood-or stool-based tests. Among them, stool-based tests detecting blood (guaiac-based fecal occult blood test-gFOBT and fecal immunochemical test-FIT), DNA, or both (multitarget FIT/DNA test) in fecal samples are current mainstream. We and other researchers in Taiwan have illustrated the performance of FIT was more specific for 90% of CRCs, adenoma and significant lower gastrointestinal lesions[4,5]. National CRC screening program is launched in Taiwan since 2004 with FIT and the actual effectiveness in reducing CRC mortality attributed to the FIT screening was 62%[6]. Stool-based tests are indeed effective. However, there remain some problems. These include sensitivity & specificity for early CRC, ideal stool sample preparation & numbers, poor at detection of adenoma, adherence to repeat testing and colonoscopy, and lack of cost-effectiveness analysis.

In contrast to stool tests, structural examinations include endoscopy (colonoscopy and flexible sigmoidoscopy) and radiological investigation (double contrast barium enema and CT colonoscopy). Although colonoscopy is more invasive, it can not only detect early lesion, distinguish lesion nature but also can resect lesions simultaneously. With improvement in image-enhanced endoscopy, colonoscopy can detect even depressed CRC, which has been reported to have lower sensitivity by FIT [7]. Endoscopy-based screening program has been initiated in my clinic since 1997. By screening 5,973 subjects (mean age: 56.6±10.7 years) from December 1997 to December 2003, I first reported the prevalence of colon polyp in Taiwan was 16.3%. Of them, 3.3% subjects had advanced polyps[8]. Form this study, we can understand that the polyp prevalence at that time is approaching the level of western countries. Not surprisingly, from year 2006, CRC has become the most common malignancy in this country.

Complete Strategy for Eliminating Cancer Should Include Primary Prevention

Although early detection and treatment has successfully decreased the incidence and mortality of CRC, complete strategy for eliminating this common lethal disease should include primary prevention (**Fig. 2**)[9]. To this purpose, identification of modifiable risk factors, irrespective of diet or lifestyle, is mandatory. In addition to providing clues for tumorigenesis, risk factors can be modified to reduce occurrence of CRC and applied to more effective or personalized screening program. To investigate risk factors of CRC, we enrolled 2,776 participants in a comprehensive health management program. Risk factors for colorectal neoplasm were determined by the multivariate regression analysis. Colorectal neoplasm were found in 605(21.8%) examinees, 68(2.5%) of whom had high-risk tumors. We found age (OR: 1.04 per year, 95% CI:1.01–1.06), male gender (OR:1.63, 95% CI:1.30–2.04), current smoker (OR: 2.14, 95% CI:1.73–2.86), HbA1c (OR: 1.22, 95% CI: 1.10–1.36), diabetes mellitus (OR: 1.48, 95% CI: 1.06–2.08) and abdominal girth (OR: 1.10/cm, 95% CI: 1.001–1.023) were risk factors

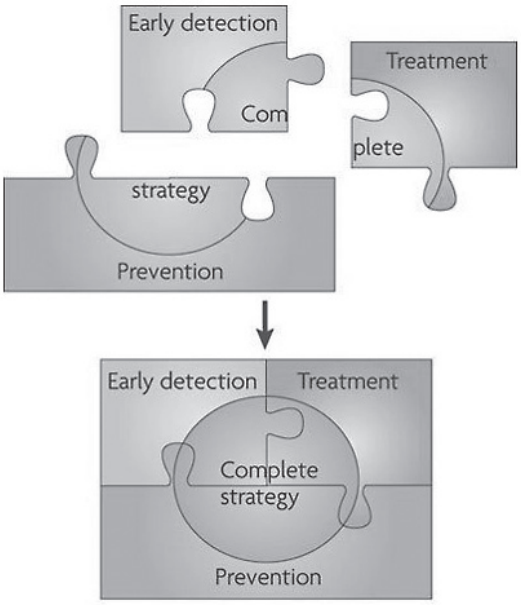

Fig. 2. Complete Strategy for Eliminating Cancer[9]

for colorectal adenomas[10]. Our research together with previous studies in this field has clearly indicated that overnutrition (such as overconsumption of energy, low level of physical activity, high BMI, abdominal obesity) leading to insulin resistance is the key risk factor for CRC.

Challenges & Opportunities: Moving Toward Personalization of CRC Screening & Integrating Primary & Secondary Prevention in Ningen Dock

In the era of precision medicine, early detection, treatment and prevention should be focused on high-risk population and screening program be more personalized. For example, metabolic syndrome and smoking significantly impact both prevalence of colorectal neoplasm and the diagnostic yield of screening tests in men aged 40 to 49 years as compared to women aged 50 to 59 years[11]. In current screening guideline, the former group is not included in screening but the latter group should be screened. In my clinic, our experience demonstrated holistic approaches (healthy living) and molecular approaches (selection of high-risk groups and target agents) may serve as a new paradigm. Therefore, further challenges in CRC prevention and screening program should move beyond one size fits all and embrace more personalized program. Furthermore, previous researches[12] also documented that screening participants do not always change their lifestyles and false health certificate effects exist. My practice in Ningen Dock show integrated approaches to combine primary and secondary prevention is the best way to optimize the efforts for improving CRC prevention and survival.

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Review Article

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The 56th Annual Scientific Meeting of Japan Society of Ningen Dock : International Session

Health Care in Taiwan, The Past and Present

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Abstract

This article is introducing Taiwan health care system, which include the evolution of Taiwan medical facilities and medical system. Health check up system and national health insurance system also in the loop of discussion. We use public nationwide data analysis and information for your reference.

Keywords Taiwan, Health Care, Health Insurance

Medical History in Taiwan

In early 20th century, top ranking disease in Taiwan area were lasted as infectious diseases, especially gastroenteritis ranked in the 1st place at that moment. During 1970s, the infection related diseases were under well control, only pneumonia remained in the Top 10 listed death of causes. Since 1990s, cerebrovascular disease, cardiovascular disease and diabetes cases rise, which were related to lifestyle. Cancer patient number incidence slowly increased at the same time.

Taiwan region also showed high incidence in chronic liver diseases and kidney disease. To prevent vertical transmission of hepatitis B virus (HBV) infection, chronic HBV carriage from perinatal mother-to-infant infection, a mass prophylaxis program was launched since July 1st 1984. In the first 15-month period of pregnant women were screened for hepatitis B surface antigen (HBsAg). HBsAg positive mother was categorized as highly infectious. Infants of highly infectious carrier mothers received an additional 0.5 mL of hepatitis B immune globulin within 24 hours after birth. Infants born to HBsAg-positive women were given 5 μg of a plasma-derived hepatitis B vaccine at ages 1.5, and 9 weeks, with a booster at age 12 months. This preventive vaccination program resulting a huge progress in the control of HBV infection in Taiwan region[1].

The HBsAg carrier rate decreased from the historical 15–20% to < 1% after vaccination. Most importantly, annual incidence of childhood hepatocellular carcinoma (HCC) has decreased from 0.67 to 0.19/100,000 children[2].

Taiwan has the highest incidence and prevalence rates of end-stage renal disease (ESRD) in the world. Prevalence of Chronic kidney disease (CKD) are reported to be 6.9% for CKD stage 3–5, 9.83% for clinically recognized CKD and 11.9% for CKD stage 1–5. Diabetes mellitus (43.2%), chronic glomerulonephritis (25.1%), hypertension (8.3%) and chronic interstitial nephritis (2.8%) are four major underlying renal diseases of ESRD. Older age, diabetes, hypertension, smoking, obesity, regular use of herbal medicine, chronic lead exposure and hepatitis C are associated with higher risk for CKD. Impact of CKD increases risk of all-cause mortality and cardiovascular diseases, especially in those with overt proteinuria and advanced CKD stages. These impacts lead to increased nationwide medical costs[3].

HCC is common in Taiwan. The incidence rates have been increasing, from about 15/100,000 in the 1980s to 30/100,000 recently. The main causes are chronic hepatitis B and C infections. Over 90% of patients positive for hepatitis B surface antigen (HBsAg) or positive to hepatitis C virus (anti-HCV). Before 1990, about 80% of patients with HCC were HBsAg positive. Because of perinatal mother-to-infant vertical transmission. HCV is the second known cause account about 70% of HBsAg negative patients. 5–10% patients have infections of both viruses.

HBV is dominantly cause HCC in the last two decades, the HCV infection has changed the clinical behavior. The proportion of anti-HCV positive cases has increased. In the areas of southern Taiwan where HCV infection now playing an important rules in HCV-associated HCC. For control hepatitis C, besides study and screening blood donors, treatment with interferon and ribavirin was implemented on a national basis since 2003. With those efforts, the government expect virus-induced HCC will be controlled and decrease the number approximately 85% patients by 2040[4].

Malignant neoplasm has become the leading cause of death in Taiwan since 1982. There has been a decreasing trend for cancers of the stomach and cervix uteri, while an increasing trend has been observed for cancers of the lung, liver, oral cavity, colon and rectum, breast and prostate.

International comparison and migrant studies have shown an elevated risk of HCC, nasopharyngeal carcinoma and cervical neoplasia in Taiwan. The national hepatitis B vaccination program, started in July 1984, has resulted in a significant decrease in childhood HCC in Taiwan. A decrease in prevalence of cigarette smoking has been observed among middle-aged men since the control of tobacco hazards was enacted in 1997. Free mass screening of cervical neoplasia and colorectal cancer has been implemented in the national health insurance (NHI) program since 1995. Project-based screening for HCC, nasopharyngeal carcinoma and breast cancer among high-risk groups was started in 1994. Most cancer patients are diagnosed by pathological examinations and treated by surgical operation, chemotherapy and radiotherapy in major teaching hospitals in Taiwan.

The Taiwan Collaborative Oncology Group has been organized to assess the efficacy of various treatment modalities through multi-centric clinical trials. Cancer researchers mainly sponsored by the National Science Council and Department of Health are engaged in basic, epidemiological and clinical studies on major cancers in Taiwan. The research include cancer genomics, gene therapy, molecular epidemiology and DNA vaccine[4].

Beginning of medical facility in Taiwan

Early stage of Taiwan medical facility was conducted by missionaries (Mackay Memorial Hospital). The original Mackay Hospital – named Mackay Clinic – was built by Mackay in Tamsui area in 1880 and named to commemorate Captain MacKay, whose widow donated the funds[5]. At that time, the Mackay Clinic was the first western medical institution in Northern Taiwan. It was temporarily closed in 1901 at the death of Mackay[6].

Mackay Hospital was reopened in 1906. In 1912, it was relocated from Tamsui to Taipei and renamed Mackay Memorial Hospital[7]. The hospital logo bears the date of the original foundation: 1880.

The Taipei tropical hospital started operations under Japanese rule in Daitōtei today's Dadaocheng as on June 18, 1895, and moved to its present location in 1898. Taipei tropical hospital was merged into Taipei Imperial University School of Medicine and renamed Taihoku Imperial University Medical School Affiliated Hospital in 1937. After the World War II, returned to Taiwan, Taipei Imperial University to be re-organized in 1945 as National Taiwan University Hospital (**Fig. 1**).

On October 19, 1991. Today, the (new) *East* and (old) *West Sites* hospital buildings have more than 4,000 employees, serving 2,000 inpatients and 8,000 outpatients daily. The hospital remains the best-known and most highly renowned medical center in Taiwan.

The hospital is a world-renowned medical center for liver diseases. Advanced surgical, angiographical, and endoscopic procedures are routinely performed (**Fig. 2**).

Training in medical physicians

Taiwanese doctors initially educated in Japanese education, the number also gradually decreased, and now the mainstream is studying in western medicine overseas. Overall, most of doctors speak English. All medical education under English textbooks to regulate the training of medical workers include a general quota of 1,300 medical students each year and special tools to manage other categories of medical workers. Post-graduate general medical training is offered to strengthen holistic care concepts and capabilities of physicians and training quality of resident physicians. In July 2011, post-graduate year (PGY) program was launched, with a total of 128

Fig. 1. Taipei Hospital, Largest Tropical Disease Hospital in Southeast Asia at that Time[8]
Source: Museum of Medical Humanities, NTUH

Fig. 2. Taipei Imperial University School of Medicine[8]
Source: Museum of Medical Humanities, NTUH

hospitals approved to conduct the program (consisting of 40 training hospitals and 88 collaborating hospitals) and participation by 1,395 students in 2014.

In order to assess better clinical skills of medical students, improve quality of clinical education, since 2013, more than 1,300 medical school graduates have passed the Objective Structured Clinical Examination (OSCE), which tests doctor-patient communication, physical examinations, and other health care techniques. Student is able to enter the second stage of the doctor's examination when they pass the OSCE qualification.

Changes in the domestic hospital

In 1970s, Taiwan entered the rapid economic-growth period of the domestic economy. 1980s number of private hospitals were founded rapidly.

Public hospital name as public hospital, National hospital, County hospital, Municipal hospital, and Military hospital. Private hospitals continue to expand their numbers in the following 30 years.

Reform public and private hospitals along with the economic growth have been conducted (renew facility, bed numbers and the management). Since 1999, Ministry of Health and Welfare take place and in charge of 29 County hospitals until now (**Table 1**, **2**).

In 2014, there were 271,555 practicing medical workers, including 62,295 physicians (Western and Chinese medicine doctors and dentists), 33,162 pharmacists, etc.

Compared to 2001, there were many medical workers in to health care system (**Table 3**).

Development of medical check up in Taiwan

The concept of health screening form in Taiwan start since 1956, officially operating in 1963 at National Taiwan University Hospital. The interest on the health check up was still far away from ideal concept. Health check up, as a self-pay product, the demand was limited. Since 1987, government established family medicine doctor specialty, promote from the government, the demand for medical examination has increased.

Table 1. Hospital Ranking in 4 Levels, Hospital Accreditation Conducted Every 4 Years[9]

Hospital level	Facility numbers
Academic Medical center	19
Regional hospital (over 250 beds)	82
Community hospital (20–250 beds)	324
Clinic (no bed)	21683
Total number include Chinese medicine	22177
Doctor numbers were 187.3 per 100,000 populations.	

Psychological department not included (Source: National statics, R.O.C, Taiwan 2015)

Table 2. Hospital Accreditation Results, 2014

Hospital Accreditation Results	Hospital Accreditation, Excellent			Hospital Accreditation, Qualified	
	Medical Centers	Regional Hospitals	District Hospitals	Regional Hospitals	District Hospitals
Quantity	19	78	49	3	275

Teaching Hospital Accreditation Results	Teaching Hospital Accreditation Results	Doctors and Medical Personnel Teaching Hospital Accreditation, Qualified	Medical Personnel (Not Doctors) – Teaching Hospital Accreditation, Qualified
Quantity	19	98	7

Taiwan Health and Welfare Report 2015, Ministry of Health and Welfare, Taiwan

Table 3. Practicing Medical Workers Number in 2014 Compared with 2001

Specialty	Number increased in 2014
Physicians	18810
Pharmacists	8271
Medical technologists	2590
Medical radiological technologists	2662
Registered nurses	59945

Taiwan Health and Welfare Report 2015, Ministry of Health and Welfare, Taiwan

In 1990s, increased demand for health check, initially the service underwent in the large scale general hospital. The hospital provides wide range service, not only health check up but also in post-check up medical care. Gradually, independent complete medical check up facility grows. Turning point noted in 1995, the start up for NHI covers the medical expenses. Covering rate from 6% until 89% nationwide. Self-pay Health check up evolve with new the business concept like, lifelong membership, family costume relationship, chain store management etc. Overnight check up program demands decreased, one day check up program is in the mainstream. Of course, the competition of each institute intensified since 1995. Management integration, M&A also appears.

Type of health check up in Taiwan

1. Public support from Health Promotion Administration
   - Every 3 years for age between 40 to 65, once a year for age over 65 citizens.
   - Basic physical examination provided for Poliomyelitis person (>35-year-old person).
   - Provide free screening for female (age 45 to 69) with mammography every 2 years.
   - Stool occult blood test (age 50 to 75) every 2 years.
   - Cervical cytology screening for women over age of 30.
   - Local government provides optional free physical examination for elderly people.
2. Responsibility for employer
   - Periodic health examination of workers under government policy.
   - Item type divided into office worker, heavy worker and food service. Hepatitis A virus (HAV) and salmonella screening for food service.
   - Health check up for foreign labors. (Infectious Disease, Tuberculosis (TB), HIV etc.)
   - Depend on individual needs and contract, company could provide financial support in advance.

For self-pay medical health check up, it was almost as same as in Japan. The estimated elderly in Taiwan will be reached 14% of the total population in 2018. Lifestyle, environmental pollution, stress, and cancer in young adult will play important role for early detection in the future.

Taiwan National Health Insurance

Taiwan launched a NHI system in 1995 after 30 years of high economic growth. Taiwan is with gross square area 36,193 km^2 land scale, about 1/10 of Japan. The population number account about 23,000,000 (1/5 of Japan). GDP per capital is 20,900 USD (year of 2014) (**Table 4**).

Since 1995, the covering rate from initial 6% until on 1995 reach to 89%, current covering rate almost 99%, include elderly, children and non-workers. NHI also covers Chinese medicine, dental care and rehabilitation program. The Basic design for Taiwan NHI is for fully coverage for medical support. For control appropriate range of medical expenses and to avoid wasting, single-payer, single-payer compulsory social insurance plan has been conducted.

For collect information, paper insurance card in initial stage was shift to IC smart card of the health insurance since the year of 2004. At the same time, electrical medical records (according ICD 9–10 codes) have been launched. Online billing process since 2006 with 99.98% achieved rate until now (**Table 5**).

Taiwan registration system

Taiwan registration system was launched since 1946, all information concentrates into one number. The registration system contain with personal household registration, birth record, name change, adoption, a personal address transfer etc.

It is as same as in Japan called "My Number Card".

Table 4. Milestone of Taiwan National Insurance

Time	Type of insurance launched
1950	Launch Labors insurance
1958	Launch Public employee insurance
1985	Launch Farmers insurance
1995	Merge all type insurances into one

Table 5. Comparison between Taiwan and Japan

	Taiwan	Japan
System	Single-payer Total expenses management	Multi-payer
Finance	Insurance fee 63.9% Public expenses 36 % self-pay, co-payment	Public expenses in 2010 account 80.3%
Ratio in GDP	6.6% (2013)	10.3% (2012)

Comparisons of NHE per Capita and GDP per Capita Between Taiwan and OECD Member States, 2012 (Source: 2014 OECD Health Data)
United States 16.9%, Germany 11.3%, Canada 10.9%, Korea 7.6%

Digitalized ID card has been launched since 2005. Digital ID card is able to apply for driver's license, income tax payment, applies for a phone number, etc. It is also implicated to health insurance system.

Changes in the health insurance system

Digital IC card launched since 2004, the aim is to collect all medical information in one place for data analysis. The smart card is a microcontroller-based card and has 32 kilobytes (KB) of memory, it will be used for four kinds of information:

1. Personal information, including the card serial number, date of issue and cardholder's name, gender, date of birth, ID number, and picture.
2. NHI-related information, including cardholder status, remarks for catastrophic diseases, number of visits and admissions, use of NHI health prevention programs, cardholder's premium records, accumulated medical expenditure records and amount of cost-sharing.
3. Medical service information, including drug allergy history and long-term prescriptions of ambulatory care and certain medical treatments. This information is planned to be gradually added depending on how health care providers adapt to the system.
4. Public health administration information (such as the cardholder's personal immunization chart and instructions for organ donation).

Shift to the smart card system has resulted in the following changes

1. Hospitals and clinics upload electronic records daily to Bureau of NHI.
2. After every six patient visits, card information is uploaded online for data analysis, audit, and authentication.
3. The reimbursement process is much easier.

Privacy and Security

Bureau of NHI has strong privacy and security requirements for the Taiwan health care smart card, including multiple smart card security mechanisms to prevent counterfeiting and protect cardholder information, mechanisms to protect the security of information during transmission, practices to prevent computer viruses and a crisis management and response plan.

The overall system architecture was designed to implement these policies, protecting the cardholder's private information while allowing access by authorized health care.

For each smart card reader, with a strict authorization and mutual authentication process to access on-card data. Cardholder personal identification numbers (PINs) designed for protect personal information.

National Health Insurance management

Taiwan NHI has their total amount budget system, annual budget usually adjust the reimbursement amount per point every year. In contrast, Japanese medical fee revised every 2 years instead. Furthermore, government launch Taiwan version of Diagnosis-related group (DRG) payment system since 2010.

Current reviews from multiple direction point of view, single payer system is able to control medical expenses. Large scale hospital get more benefit from those system compared with small sized hospital. Using IC card is able to collect big data for major analysis. And government is able to maintain management by data analysis.

Even with those effort, unfortunately several burden occur. Due to the concept of "Free for service", patient seeking medical service without any control demand. The total medical expenditure increase from 26.4 billion USD (2007) to 610.1 billion USD (2014). Annual average number of outpatient department visit per capita is 15.2 visits in 2014. In 2014, there were 357.01 million outpatient visits and 3.20 million hospital admissions. Averages length of hospitalization of 1.3 days[10].

Leading Causes of Death

Economic transformation, better quality of life, and improved health care have led to dramatic changes in the leading causes of death. In 1952, acute and communicable diseases took the most lives in Taiwan; today, malignant neoplasms, cardiovascular disease, and accidents are the main culprits. In 2014, there were 162,911 deaths, and the crude mortality rate was 696.1 per 100,000 population, an increase of 5.3% compared to 2013, and an increase of 17.9% compared to 2004. The standardized mortality rate (based on the WHO standard world population age structure for 2000) was 443.6 people per 100,000 population, an increase of 1.9% compared to 2013, and a decrease of 16.1% compared to 2004[10].

In 2014, the 10 leading causes of death accounted for 77.5% of all deaths and were primarily chronic diseases as below (**Table 6**).

Compared to 2004, pneumonia and hypertensive diseases rise in the rankings; diabetes mellitus, accidents and adverse effects, chronic liver disease and cirrhosis, and nephritis, nephrotic syndrome goes down.

Cancer Incidence and Causes of Cancer Death

1. Cancer Incidence

According to 2012 cancer registry data, the crude incidence rates of cancer for males and females were 458.8 and 370.6 people per 100,000 populations. If adjustments are made based on the WHO-constructed standard world population age structure from 2000, the age-standardized incidence rates for males and females were to 341.4 and 263.3 people per 100,000 population.

Table 6. Leading Causes of Death in Taiwan, 2014

Ranking	Disease
1	Malignant neoplasms
2	Cardiovascular Diseases (except hypertensive diseases)
3	Cerebrovascular diseases
4	Pneumonia
5	Diabetes mellitus
6	Accidents and adverse effects
7	Chronic lower respiratory diseases
8	Hypertensive diseases
9	Chronic liver disease and cirrhosis
10	Nephritis, nephrotic syndrome

Source: Taiwan Health and Welfare Report 2015

Table 7. The 10 Leading Causes of Cancer Death in 2014

Ranking	Cancer
1	Cancers of the lung
2	Cancers of the liver
3	Cancers of the colon, rectum, and anus
4	Cancers of the breast (female)
5	Cancer of the oral cavity
6	Cancer of the prostate
7	Cancer of the stomach
8	Cancer of the pancreas
9	Cancer of the esophagus
10	Cancers of the cervix and uterus

Source: Taiwan Health and Welfare Report 2015

Table 8. Population Status of Major Countries

	2013 Total Fertility Rate	2013 Crude Birth Rate	2013 Crude Death Rate	2013 rate of Natural Increase
	(Per Women)	‰	‰	%
Global	3.0	23	8	1.5
Taiwan	1.1	9	7	0.2
Japan	1.4	8	10	−0.2
Korea	1.3	10	6	0.4
United States	2.0	13	8	0.5

Source: 2015 WHO Statistical Information System

Causes of Cancer Death

In 2014, there were 46,095 cancer deaths. This accounted for 28.3% of total deaths and a crude mortality rate of 197.0 per 100,000 population increase of 22.7% compared to 2004. The standardized cancer mortality rate in 2014 was 130.2 per 100,000 population, a decrease of 0.2% compared to 2013, and a drop of 8.8% compared to 2004. When compared to 2004, Cancer of oral cavity, Cancer of prostate, and Cancer of pancreas increased in the rankings, Cancer of stomach and Cancers of cervix uteri and uterus falls (**Table 7**)[10].

Birth and Death

Changes in social values led to annual decreases in the fertility rate, with the crude birth rate (live births per 1,000 population) falling from 11.7‰ in 2001 to 9.0‰ in 2014. The crude death rate (total number of deaths per 1,000 population) rose from 5.7‰ in 2001 to 7.0‰ in 2014. The rate of natural increase (crude birth rate minus crude death rate) fell to a record low of 0.9‰ in 2010 before rising to 2.0‰ in 2014 (**Table 8**)[10].

Accelerated aging society in Taiwan

At the end of 2014, Taiwan had a registered population of 23 million, consisting of 12 million males and 12 million females. The sex ratio (ratio of males to females normalized to 100) was 99.7, and annual population growth was 2.6 ‰. Between 2004 and 2014, the gradually declining birth rate caused the proportion of the population aged 14 and younger to drop and the proportion of the population aged 65 and older to increase during the same period. Historic age structure data show that the percentage of the population aged 65 and older reached 7% in 1993, making Taiwan an aged society. The percentage of the population aged 14 and younger dropped from 20.8% in 2001 to 14.0% in 2014. During the same period, the proportion of the population aged 65 and older increased from 8.8% to 12.0%.

The dependency ratio, (people aged 14 and younger and 65 and older) to the working-age population (those aged 15–64), fell from 42.1% in 2001 to 35.1% in 2014. The decline can be attributed to the rapid decrease in the young age dependency ratio (the ratio of dependents aged 14 and younger to the population aged 15–64) and the steady increase in the old age dependency ratio (ratio of population aged 65 and older to the population aged 15–64) (**Table 9**)[10].

Table 9. Dependency Ratios of Major Countries (Unit: %)

	1960	1970	1980	1990	2000	2005	2010	2013
Taiwan	92.0	74.2	57.3	49.9	42.3	39.7	35.8	34.9
Japan	56.0	45.3	48.4	43.4	46.6	50.7	56.9	61.6
Korea	80.7	83.3	60.7	44.1	39.5	39.6	37.6	37.1
United States	66.5	61.4	51.3	51.9	50.9	48.9	49.0	50.4

Source: The World Bank

Life Expectancy

According to estimates, the life expectancy at birth for both sexes was 79.8 in 2014, an increase of 2.3 years compared to 10 years earlier. For males in the same period, life expectancy at birth increased by 2.0 years to 76.7, and for females it increased by 2.4 years to 83.2. The higher increase for females caused the life expectancy gap between the sexes to widen.

65 years of age or of the elderly population of Taiwan is more than 7% in 1993, by 2018 expected to reach 14% of the total population. We expected aging population reach 20% of the total population on 2025. Estimated Labor force (age of 15 until age of 64) against over 65 aged population from 7 against 1 to 4 against 1 in 2022, will be 2 against 1 in yeas of 2039. In order to raise the quality of life of older people and reduce the threat of chronic diseases, Taiwan promotes age-friendly cities, age-friendly health care, health promotion among elderly persons, prevention program of major chronic diseases, and prevention of cancer. In the future, we are going to launch Long term care program for the coming aging society as the aging population is expecting reach to 25% in 20 years.

New demands in the future

Our new medical demand associated with the rapid aging society in Taiwan will be listed as below:

- Cancer screening
- Diversified demand associated with the difference in gender
- Diverse demand of health and welfare
- Prevention of organ associated aging
- "Team medical care"
- Prevention medicine
- Nursing for elderly, Long term care

The future challenge:

- Promote the lifestyle or fill the life quality in health preventive medicine.
- Demand for customized medical examination.
- Gender, aging, organ-specific, comprehensive life improvement.
- Long term care insurance will be next challenge.

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Review Article

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High-sensitivity C-reactive Protein and Serum Uric Acid are Predictors of Incident Metabolic Syndrome

Eiji Oda

Abstract

Metabolic syndrome (MetS) is a constellation of interrelated metabolic risk factors that appear to promote the development of type 2 diabetes and cardiovascular disease (CVD). MetS may be a systemic manifestation of adipose tissue inflammation with ectopic lipid accumulation in the liver and skeletal muscle which is related to many other complex pathophysiological mechanisms including insulin resistance, endothelial dysfunction and oxidative stress. In this review, longitudinal associations between baseline high-sensitivity C-reactive protein (hs-CRP) as well as serum uric acid, both of which are known to be associated with MetS from cross-sectional studies, and incidence of MetS are discussed. In conclusion, hs-CRP and uric acid are significant predictors of incident MetS. However, hs-CRP should be evaluated two or more times at baseline because the level of hs-CRP widely fluctuates then. Our findings suggest that hypouricemic agents may be useful for reducing risk of MetS and CVD in patients with hyperuricemia.

Keywords metabolic syndrome, hs-CRP, serum uric acid

Metabolic syndrome (MetS)[1–6] is a constellation of interrelated metabolic risk factors that appear to directly promote the development of type 2 diabetes and cardiovascular disease (CVD). Although there had been controversy regarding the criteria for MetS, several academic societies adopted the revised National Cholesterol Education Program (NCEP) criteria[5] in order to harmonize criteria for MetS worldwide in 2009[6]. However, some professional societies argued that no existing definition of MetS meets the criteria of a clinical syndrome[7] and the WHO Expert Consultation reported that MetS has limited practical utility in clinical practice and epidemiological studies[8]. MetS may be a systemic manifestation of adipose tissue dysfunction characterized by increased aggregation of activated macrophages in adipose tissue[9,10] with ectopic lipid accumulation in the liver and skeletal muscle[11] induced by chronic energy overload, which is related to many other complex pathophysiological mechanisms including insulin resistance, endothelial dysfunction and oxidative stress[12,13]. Inflammation is thought to be a core mechanism of both MetS[9–14] and CVD[15]. In this review, longitudinal associations between baseline high-sensitivity C-reactive protein (hs-CRP) as well as serum uric acid[16], both of which are known to be associated with MetS from cross-sectional studies, and incidence of MetS are discussed.

High-sensitivity C-reactive protein (hs-CRP)

An increased number of crown-like structures composed of a large number of activated macrophages surrounding enlarged dead adipocytes has been shown to be a characteristic histological feature of adipose tissue dysfunction[10]. Adipose expression of tumor necrosis factor-α plays a direct role in obesity-linked insulin resistance[14]. MetS may be a systemic manifestation of adipose tissue dysfunction[9,10] with ectopic lipid accumulation in the liver and skeletal muscle[11] and is related to many other complex pathophysiological mechanisms such as systemic inflammation[13], insulin resistance[17], and endothelial dysfunction[12].

Cross-sectional associations between hs-CRP and MetS and its components are well-known[18,19]. Ridker *et al.*[20] proposed that hs-CRP should be added to the clinical criteria of MetS. Regarding longitudinal studies, elevated levels of hs-CRP have been seen to predict future MetS independently of age, sex, and smoking in apparently healthy Koreans[21]. Also, the relative risks of future MetS in the highest quartile of hs-CRP at baseline was 2.4 (95% CI, 1.3–4.2) compared to subjects in the lowest

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quartile. Positive associations persisted after adjustment for age, sex and smoking; the multivariate relative risks for the highest vs. lowest quartiles was 2.3 (95% CI, 1.3–4.1; *p* for trend=0.005)[21]. We previously demonstrated that both hs-CRP and white blood cell count are equally significant but poor predictors of incident MetS in a Japanese health screening population where obesity is not prevailing[22] while hs-CRP was superior to white blood cell count as an inflammatory component of MetS in a cross-sectional study[18]. Neither hs-CRP nor white blood cell count was an independent predictor of MetS after further adjustment for the baseline components of MetS[22]. Also, the greater chronological changes in hs-CRP values than in white blood cell count in the above longitudinal study[22] could reduce the superiority of hs-CRP to white blood cell count as a predictor of incident MetS.

Annual fluctuations in cardiometabolic risk factors are presented in **Table 1**, which were calculated based on data from 2,371 individuals who visited our health check-up center. Inflammatory markers are weak predictors of MetS in Japanese where the prevalence of obesity is very low compared to other developed societies. However, although hs-CRP levels in Japanese are substantially lower than those in Westerners[18,20], very low levels of hs-CRP have been found to be significantly associated with other metabolic risk factors in Japanese [19].

Serum uric acid

Associations of gout with hypertension, diabetes, kidney disease, and CVD have been observed since the late 19th century[23]. Since Gertler *et al.* studied the association between serum uric acid (UA) and coronary heart disease (CHD)[24] and Cannon *et al.* reported the association between hyperuricemia and hypertension[25], a number of epidemiological studies have been conducted on the association between UA and CVD including stroke[26], CHD[27], childhood hypertension[28], kidney disease[29,30], and MetS[31,32]. Although UA is associated with CVD, some experts have argued that it is not a risk factor of CVD and clinicians should not rely on UA in patient assessment[33] and major professional societies have not considered UA as a cardiovascular risk factor[34,35]. However, some studies that have adjusted for multiple risk factors suggest that UA is an independent risk factor of CVD[36–38], kidney disease [39,40], hypertension[41–48] and diabetes[49–55]. The increased serum UA levels observed in MetS have been attributed to hyperinsulinemia because insulin reduces the renal excretion of UA[56]. However, hyperuricemia often precedes the development of hyperinsulinemia[57] and diabetes[49–55].

Animal studies show that decreasing UA levels can prevent or reverse features of MetS[58–60]. Nakagawa *et al.* suggested that UA may be a cause of MetS, possibly due to its ability to inhibit endothelial function and that fructose may have a major role in the epidemic of MetS and obesity due to its ability to raise UA[32,58]. Normalization of plasma UA with a selective xanthine oxidase inhibitor in rats with MetS alleviated both metabolic and glomerular hemodynamic and morphological alterations[59]. Allopurinol reduced serum levels of UA and ameliorated features of MetS such as hypertension, hypertriglyceridemia, hyperglycemia, and insulin resistance in hyperuricemic rats on high-fructose diets and given thiazides[60].

A number of epidemiological studies have demonstrated a cross-sectional association between UA and MetS[61–64]. However, longitudinal studies regarding baseline UA as a predictor of MetS are limited[65–69]. Ryu *et al.* reported that, among a variety of candidate risk factors, baseline UA, weight change, gamma-glutamyltransferase, and alanine aminotransferase were independent predictors of MetS in Korean male workers[65]. Sui *et al.* reported that men with UA of ≥6.5 mg/dL (upper third) had a 1.60-fold increase in risk of MetS (95% CI, 1.34–1.91)

Table 1. Annual Variations in Cardiometabolic Risk Factors

	coefficients of annual variation [a]
high-sensitivity CRP	4.215
white blood cell count	0.197
body mass index	0.043
systolic blood pressure	0.096
diastolic blood pressure	0.099
fasting plasma glucose	0.094
hemoglobin A1c	0.045
triglycerides	0.545
HDL cholesterol	0.126
LDL cholesterol	0.165
uric acid	0.137

[a] standard deviations of the annual change divided by the mean

as compared with those who had UA of <5.5 mg/dL (lowest third) while women with UA of ≥4.6 mg/dL had at least a 2-fold higher risk of MetS (p for trend=0.02) in the US[66]. Gonçalves *et al.* reported that, using a multivariate approach, baseline hyperuricemia defined as ≥ 7.0 mg/dL in men and ≥ 6.0 mg/dL in women was positively associated with MetS incidence rate ratios (IRR, 1.73; 95% CI, 1.08–2.76) and each 1 SD increase in baseline UA was associated with a 1.22-fold increase in MetS risk (IRR, 1.22; 95% CI, 1.05–1.42) in the non-institutionalized resident population of Porto, Portugal[67]. Yang *et al.* reported a significantly stepwise increase in the incidence of MetS across tertiles of baseline UA (p for trend <0.001) in a Chinese population[68]. After adjusting for age, blood pressure, triglycerides, HDL cholesterol, fasting glucose, and waist circumference, women, but not men, in the middle and upper tertiles of baseline UA had a significantly higher risk of developing MetS when compared with subjects in the lowest tertile (hazard ratio, 1.67; 95% CI, 1.12–2.49 and hazard ratio, 3.18; 95% CI, 2.20–4.60, respectively)[68]. In our longitudinal study among apparently healthy Japanese, UA was a significant predictor of MetS in both men and women after adjusting for the pre-existing components of MetS and other confounding covariates[69]. However, no significant association was found between longitudinal changes in UA and incident MetS either in men or women[69]. Ferrara *et al.* analyzed 1,499 American Indians without diabetes or MetS who were divided into sex-specific tertiles of UA, where the third tertile (group H) was compared with the first two tertiles (group N). They reported that incident MetS after 4-year follow-up was more frequent in the highest tertile of UA than the first two tertiles (odds ratio (OR), 1.44; 95% CI, 1.10–1.91; $p < 0.01$) in American Indians without diabetes or MetS[70]. This association was still significant (OR = 1.13, $p = 0.04$) after adjusting for family relatedness, sex, history of hypertension, insulin resistance, central adiposity and renal function, but disappeared after further adjustment for fat-free mass[70]. Yadav *et al.* reported that subjects in the fifth quintiles of UA had significantly higher ORs for incident MetS after adjustment for age, total cholesterol and low-density lipoprotein cholesterol during a mean of 2.6 years of follow-up in Korean men and women and that the association between hyperuricemia and incident MetS was stronger in women than men.[71]. These studies suggest that UA is a risk factor of MetS. Although further studies are required to elucidate ethnic, age, and gender differences regarding the association between UA and incident MetS, management of hyperuricemia could be beneficial in preventing CVD-related morbid conditions in patients[16].

Conclusions

hs-CRP and UA are significant predictors of incident MetS. However, at baseline, hs-CRP should be evaluated two or more times because the level of hs-CRP widely fluctuates then. Our findings suggest that hypouricemic agents may be useful for reducing the risk of MetS and CVD as well as for patients with hyperuricemia.

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Original Article

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Small-dense LDL Cholesterol is Associated with Insulin Resistance in BMI < 30 kg/m^2, Non-diabetic Japanese Population

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Abstract

Aims: Small-dense low-density lipoprotein (sdLDL) and malondialdehyde LDL (MDA-LDL) are considered more atherogenic than LDL. However, information on the major determinants of sdLDL cholesterol (sdLDL-C) and MDA-LDL levels in Japanese subjects without diabetes is limited.

Methods: This study included 870 non-diabetic subjects with a body mass index (BMI) <30 kg/m^2. All subjects underwent an annual health check-up that included sdLDL-C and MDA-LDL analyses.

Results: When subjects were stratified into four groups according to homeostasis model assessment of insulin resistance (HOMA-IR), sdLDL-C and MDA-LDL levels increased significantly, relative to the reference, with increasing HOMA-IR values, whereas LDL-C levels showed no consistent increase with increasing HOMA-IR. Multiple linear regression and logistic regression analyses revealed that LDL-C and triglyceride (TG) levels were major determinants of sdLDL-C levels, whereas LDL-C, sdLDL-C and high-density lipoprotein cholesterol (HDL-C) levels were major determinants of MDA-LDL levels.

Conclusions: Our data suggest that an increase in the LDL-C level and insulin resistance may lead to an increase in sdLDL-C levels and that increases in the LDL-C and sdLDL-C levels may lead to an increase in MDA-LDL in Japanese subjects without diabetes.

Keywords small-dense LDL, insulin resistance, MDA-LDL, annual health check-up

The correlation between hypercholesterolemia and the risk of coronary heart disease (CHD) suggests that reduced serum total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) levels result in a reduced risk of CHD[1–5]. LDL-C comprises multiple distinct subclasses of particles that differ in size, density, physicochemical composition, metabolic behavior, and atherogenicity[6]. Small-dense LDL (sdLDL) indicates particles that are small in diameter and high in density within the LDL class. Plasma sdLDL-C levels have been found to be strongly correlated with an atherogenic lipid profile and higher in patients with diabetes mellitus than in those without diabetes mellitus[7]. In a model that included established risk factors, sdLDL-C was associated with incident CHD, with a hazard ratio of 1.51 for the highest versus the lowest quartile. Even among individuals considered to have a low cardiovascular risk based on their LDL-C levels, the sdLDL-C level predicted a risk of incident CHD, with a hazard ratio of 1.61[7]. In addition, sdLDL is strongly associated with various types of CHD, and this association is independent of traditional and nontraditional coronary risk factors, suggesting that this lipid parameter may be a better predictor of CHD risk than LDL-C levels[8]. Many studies have shown elevated sdLDL levels in patients with atherosclerotic disorders, such as dyslipidemia, diabetes, metabolic syndrome (MetS), and cardiovascular disease[9–16].

Malondialdehyde LDL (MDA-LDL), also known as oxidized LDL, might play a key role in the progression of atherosclerosis[17,18]. Previous studies have reported associations of increased serum MDA-LDL levels with CAD[19–21] or coronary artery calcification[22]. Serum MDA-LDL levels have also been positively correlated with the carotid intima-media thickness[20,23]. It has been found that the MDA-LDL concentration is highest in the already highly proatherogenic sdLDL fraction[24], suggesting that sdLDL is particularly vulnerable to MDA-mediated oxidation[25].

MetS is a multidimensional risk factor for atherosclerotic CHD[26]. The definition of dyslipidemia includes TG level ≥150 mg/dL and high-density lipoprotein cholesterol (HDL-C) level <40 mg/dL but does not include

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LDL-C criteria. Therefore, MetS represents a high CHD risk state often accompanied by insulin resistance, regardless of LDL-C levels.

Obesity and insulin resistance have been linked with alterations in the lipoprotein particle profile and may, therefore, influence the risks of CHD and type 2 diabetes mellitus[27,28]. Obesity, insulin resistance, and diabetes are closely related. On the other hand, >20% of subjects with a normal weight were found to be metabolically unhealthy[29] so it is important to consider the possibility that non-obese subjects without diabetes could have high levels of sdLDL-C and MDA-LDL, which are considered to be more atherogenic than LDL[7,17,18]. However, information on the relationship between sdLDL-C and insulin resistance in non-obese subjects without diabetes is limited. In addition, the relationship between sdLDL-C and MDA-LDL is uncertain.

This study aimed to clarify the major determinants of sdLDL-C and MDA-LDL levels in Japanese subjects without diabetes.

Methods

Subjects

A total of 944 subjects underwent annual health checkups at the Health Evaluation and Promotion Center, Tokai University Hachioji Hospital between April 2011 and March 2014. These examinations included sdLDL-C and MDA-LDL analyses. After excluding 76 subjects with fasting plasma glucose (FPG) levels ≥126 mg/dL, 55 subjects with HbA1c levels ≥6.5%, 41 subjects receiving treatment for diabetes mellitus, and 33 subjects with body mass index (BMI) ≥30 kg/m^2, the final number of subjects included in this study was 870. Medical history information was obtained via self-administered questionnaires and interviews conducted by nurses. Among the 870 subjects, 207 were using antihypertensive drugs, and 151 were using medications for dyslipidemia.

Measurements

Waist circumference (WC) was measured at the level of the umbilicus while the subject was standing and during slight expiration. Blood pressure (BP) was measured on the upper right arm with an automatic blood pressure monitor (TM-2655P; A&D, Tokyo, Japan) while the subject was seated. Blood samples were collected early in the morning after an overnight fast. Fasting immunoreactive insulin (FIRI) levels were measured using a fluorescence enzyme immunoassay (ST AIA-PACK IRI; Toso, Tokyo, Japan). The homeostasis model assessment of insulin resistance (HOMA-IR) was calculated as follows: FPG (mg/dL) × FIRI (mU/mL)/405[30]. LDL-C was calculated using the Friedewald formula[31]. HDL-C and TG levels were measured via visible spectrophotometry (Determiner L HDL-C, and Determiner L TG II, respectively; Kyowa Medex, Tokyo, Japan). SdLDL-C levels were measured using a homogeneous method (sd LDL-Ex; DENKA SEIKEN, Tokyo, Japan). MDA-LDL levels were measured by enzyme-linked immunosorbent assay (ELISA), using monoclonal antibodies specific for MDA-LDL (ML25) and to apolipoprotein B (AB16) (Product name Sekisui Medical, Tokyo, Japan). High-molecular-weight adiponectin (HMW-Ad) was measured by chemiluminescent enzyme immunoassay, using a monoclonal antibody to human HMW-Ad (Product name Fujirebio, Tokyo, Japan).

Verbal consent for the analytical use of anonymized health records was obtained from all subjects. The study protocol was approved by the institutional ethics committee of the Tokai University School of Medicine.

Statistical analysis

The significance of pairwise comparisons was determined using the *t*-test. Associations between HOMA-IR and various parameters and comparisons of mean values among more than two groups were performed using Dunnett's multiple comparisons test, using subjects with HOMA-IR 1.0 to <1.7 as the reference group. A multiple linear regression analysis was performed to identify significant determinants of sdLDL-C and MDA-LDL. For sdLDL-C, WC, systolic BP, diastolic BP, FPG, FIRI, LDL-C, HDL-C, TG, and HMW-Ad were used as independent variables. For MDA-LDL, sdLDL-C was included as an independent variable in addition to the variables listed for sdLDL-C. We then performed a multiple logistic regression analysis to calculate odds ratios (ORs) for the upper tertile of sdLDL-C (men: ≥36 mg/dL, women: ≥31 mg/dL) and MDA-LDL (men: ≥137 U/L, women: ≥120 U/L) levels, using the same variables listed for the multiple linear regression analysis. A stepwise procedure was used to select variables for the multiple linear and logistic regression analyses. Statistical analyses were performed using SAS software, version 9.3 (SAS Institute Inc., Cary, NC, USA). All *p*-values were two-tailed, and a *p*-value <0.05 was considered statistically significant.

Results

Table 1 lists the subjects' characteristics. The BMI, WC, BP, FPG, HOMA-IR, TG, sdLDL-C, and MDA-LDL values were significantly higher in men than in women. In contrast, the age, HDL-C, LDL-C, and HMW-Ad values were significantly higher in women than in men.

Table 2 lists the subjects' characteristics after stratification by sex and HOMA-IR. The BMI, WC, BP, FPG and TG values, all of which were associated with diagnostic components of MetS, increased as the HOMA-IR increased. SdLDL-C, and MDA-LDL levels also increased as the HOMA-IR increased. This is in contrast to the results for LDL-C, which showed that the LDL-C levels of male subjects with HOMA-IR of 1.0< and≥1.7 and female subjects with HOMA-IR of ≥1.7 were not

Table 1. Characteristics of Study Subjects

	Men (n = 546)	Women (n = 324)	p
Age (years)	58.4 ±12.1	60.1 ±11.5	0.042
BMI (kg/m^2)	23.8 ±2.7	21.6 ±2.6	<0.001
Waist circumference (cm)	84.4 ±7.5	78.7 ±8.2	<0.001
HMW-Ad (μg/mL)	2.87 ±1.91	6.13 ±3.75	<0.001
Systolic BP (mmHg)	123.7 ±16.1	118.8 ±18.6	<0.001
Diastolic BP (mmHg)	79.6 ±12.0	72.0 ±12.0	<0.001
FPG (mg/dL)	101.0 ±8.1	96.7 ±8.1	<0.001
HOMA-IR	1.53 ±1.03	1.23 ±0.80	<0.001
TG (mg/dL)	123.5 ±152.8	92.1 ±53.9	<0.001
HDL-C (mg/dL)	59.4 ±14.2	75.4 ±16.5	<0.001
LDL-C (mg/dL)	122.8 ±28.2	127.6 ±32.3	0.023
SdLDL-C (μg/dL)	38.2 ±15.5	33.2 ±12.9	<0.001
MDA-LDL (U/L)	142.2 ±41.6	126.9 ±41.4	<0.001

Variables are given as means ± standard deviations.
HMW-Ad, high-molecular-weight adiponectin; BP, blood pressure; HOMA-IR, homeostasis model assessment-insulin resistance calculated by Friedewald formula; sdLDL-C, small-dense low-density lipoprotein cholesterol; MDA-LDL, malondialdehyde low-density lipoprotein

Table 2. Characteristics of Study Subjects Stratified by HOMA-IR

(a) Men

	<1.0 (n=169)	1.0 – <1.7 (n=189)	≥1.7 (n=184)
Age (years)	59.7 ±11.9	59.3 ±12.5	56.4 ±11.8*
HOMA-IR	0.67 ±0.19**	1.28 ±0.20	2.54 ±1.13**
BMI (kg/m^2)	22.1 ±2.4**	23.5 ±2.3	25.6 ±2.6**
Waist circumference (cm)	79.8 ±6.7**	83.5 ±6.5	89.4 ±6.0**
HMW-Ad (μg/mL)	3.72 ±2.33**	2.9 ±1.73	2.10 ±1.26*
Systolic BP (mmHg)	122.1 ±15.1	122.5 ±17.1	126.3 ±15.8*
Diastolic BP (mmHg)	78.8 ±11.2	78.5 ±13.0	81.4 ±11.6*
FPG (mg/dL)	97.6 ±8.2**	100.8 ±7.4	104.1 ±7.4**
TG (mg/dL)	110.5 ±247.1	116.5 ±59.2	142.0 ±95.5
HDL-C (mg/dL)	64.2 ±14.0*	60.4 ±13.9	54.2 ±13.0
LDL-C (mg/dL)	114.4 ±31.4	121.3 ±28.7	120.3 ±29.2
SdLDL-C (μg/dL)	32.9 ±13.6**	39 ±14.7	42.3 ±16.5
MDA-LDL (U/L)	130.5 ±36.3**	143.9 ±43.6	150.9 ±41.9

(b) Women

	<1.0 (n=133)	1.0 – <1.7 (n=127)	≥1.7 (n=64)
Age (years)	58.6 ±11.3	61.0 ±12.3	61.7 ±9.9
HOMA-IR	0.65 ±0.20**	1.25 ±0.19	2.37 ±1.05**
BMI (kg/m^2)	20.3 ±2.2**	22.0 ±2.2	23.6 ±2.5**
Waist circumference (cm)	74.2 ±7.0**	80.2 ±6.9	85.0 ±7.9**
HMW-Ad (μg/mL)	7.74 ±4.29**	5.44 ±2.96	4.05 ±2.20*
Systolic BP (mmHg)	115.3 ±17.2	119.1 ±18.1	125.1 ±20.8
Diastolic BP (mmHg)	71.2 ±12.1	71.4 ±10.7	74.8 ±14.0
FPG (mg/dL)	92.5 ±6.6**	98.2 ±6.7	102.6 ±8.6**
TG (mg/dL)	78.1 ±39.2	93.1 ±42.7	119.1 ±82.9**
HDL-C (mg/dlL)	79.6 ±16.2*	74.4 ±15.9	68.9 ±16.3
LDL-C (mg/dL)	118.9 ±29.1*	129.8 ±34.6	133.6 ±32.8
SdLDL-C (μg/dL)	29.9 ±11.4*	33.4 ±12.2	40.3 ±14.4**
MDA-LDL (U/L)	114.0 ±33.8**	130.6 ±43.2	146.3 ±43.6*

Subjects were stratified into four groups according to HOMA-IR.
Variables are given as means ± standard deviations.
HOMA-IR, homeostasis model assessment-insulin resistance; HMW-Ad, high-molecular-weight adiponectin; BP, blood pressure calculated by Friedewald formula; sdLDL-C, small-dense low-density lipoprotein cholesterol; MDA-LDL, malondialdehyde low-density lipoprotein
**p < .01, *p < .05 by Dunnett's multiple comparison test, HOMA-IR 1.0 - <1.7 used as a reference.

significantly different from those of the reference group (HOMA-IR of 1.0 to <1.7). The HDL-C and HMW-Ad decreased as the HOMA-IR increased.

Table 3 shows the results of a multiple linear regression analysis for sdLDL-C and logistic regression analysis for the upper tertile of sdLDL-C. Five of the nine variables listed in the table were selected, four of which were the same for men and women. Among the selected variables in the multiple linear regression analysis, LDL-C and TG were also selected for both genders in the logistic regression analysis for the upper tertile of sdLDL-C. Standardized regression coefficients in the multiple regression analysis were higher for LDL-C and TG than for the other selected variables.

Fig. 1 is a bar graph representation of sdLDL-C levels when subjects were stratified according to LDL-C (three groups: LDL-C of 0 to <140, 140 to <160, ≥160 mg/dL) and TG (two groups: TG of <150, ≥150 mg/dL) levels. Numbers on the bars are the mean values of each group. Briefly, sdLDL-C levels increased as LDL-C, and TG levels increased in both men and women.

Table 4 shows the results of a multiple linear regression analysis for MDA-LDL and a logistic regression analysis for the upper tertile of MDA-LDL. Five variables of the ten listed in the table were selected, three of which were the same for men and women. Among the variables

Table 3. Multiple Linear Regression Analysis for sdLDL-C and Multiple Logistic Regression Analysis for Upper Tertile of sdLDL-C Giving Odds Ratios and 95% Confidence Intervals

(a) Men

	Multiple Linear Regression				Multiple Logistic Regression				
	RC	SRC	t	*p*	RC	SE	OR	95% CI	*p*
LDL-C	0.332	0.633	21.41	<.001	0.063	0.00654	1.065	1.051–1.079	<.001
TG	0.057	0.567	18.71	<.001	0.037	0.00377	1.038	1.030–1.045	<.001
HMW-Ad	−1.306	−0.160	−5.53	<.001		---------- not selected ----------			
FPG	0.174	0.091	3.17	<.001		---------- not selected ----------			
Diastolic BP	0.098	0.076	2.65	0.008	0.025	0.0107	1.025	1.004–1.047	0.019

Variables were selected by a stepwise procedure.
sdLDL-C, small-dense low-density lipoprotein cholesterol; RC, regression coefficient; SRC, standardized regression coefficient; SE, standard error; OR, odds ratio; CI, confidence interval calculated by Friedewald formula; HMW-Ad high-molecular-weight adiponectin; BP, blood pressure

(b) Women

	Multiple Linear Regression				Multiple Logistic Regression				
	RC	SRC	t	*p*	RC	SE	OR	95% CI	*p*
LDL-C	0.258	0.649	21.99	<.001	0.0705	0.00809	1.073	1.056–1.090	<.001
TG	0.120	0.504	16.79	<.001	0.0300	0.00475	1.030	1.021–1.040	<.001
FPG	0.174	0.109	3.59	<.001		---------- not selected ----------			
HMW-Ad	−0.264	−0.076	−2.49	0.014		---------- not selected ----------			
WC	−0.103	−0.066	−2.03	0.043		---------- not selected ----------			

Variables were selected by a stepwise procedure.
sdLDL-C, small-dense low-density lipoprotein cholesterol; RC, regression coefficient; SRC, standardized regression coefficient; SE, standard error; OR, odds ratio; CI, confidence interval calculated by Friedewald formula; HMW-Ad, high-molecular-weight adiponectin; WC, waist circumference

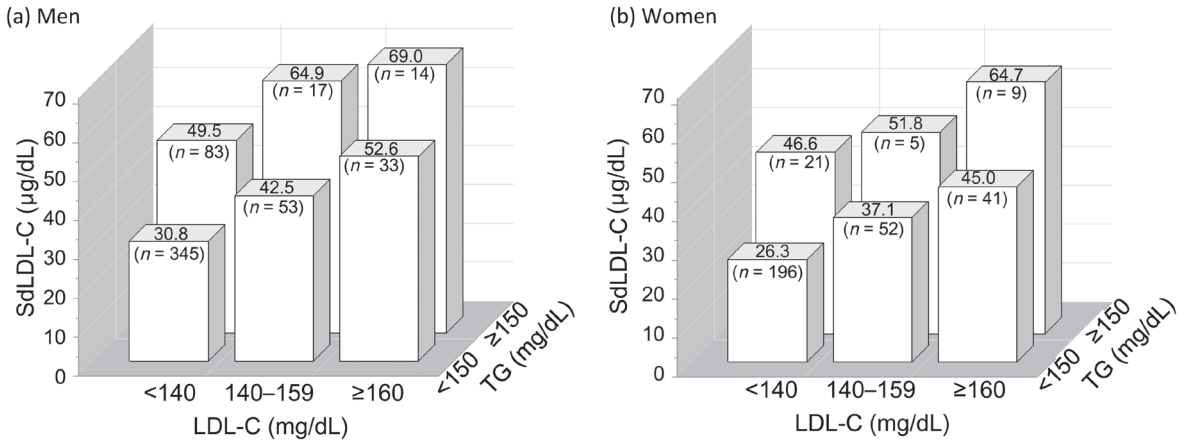

Fig. 1. Bar Graph of Mean sdLDL-C Values After Stratifying Subjects According to Sex, LDL-C and TG Levels
Numbers on bars are mean values of each group (mg/dL). sdLDL-C, small-dense low-density lipoprotein cholesterol

Table 4. Multiple Linear Regression Analysis for MDA-LDL and Multiple Logistic Regression Analysis for Upper Tertile of MDA-LDL Giving Odds Ratios and 95% Confidence Intervals

(a) Men

	Multiple Linear Regression				Multiple Logistic Regression				
	RC	SRC	t	*p*	RC	SE	OR	95% CI	*P*
LDL-C	0.639	0.452	13.35	<.001	0.033	0.005	1.034	1.024–1.043	<.001
SdLDL-C	0.948	0.352	9.58	<.001	0.063	0.010	1.065	1.045–1.086	<.001
HDL-C	−0.461	−0.147	−4.65	<.001	−0.019	0.008	0.961	0.966–0.996	0.016
Diastolic BP	0.265	0.076	2.52	0.012		---------- not selected ----------			
HMW-Ad	−1.056	−0.048	−1.50	0.135		---------- not selected ----------			

Variables were selected by a stepwise procedure.
MDA-LDL, malondialdehyde low-density lipoprotein; RC, regression coefficient; SRC, standardized regression coefficient; SE, standard error; OR, odds ratio; CI, confidence interval calculated by Friedewald formula; sdLDL-C, small-dense low-density lipoprotein cholesterol; BP, blood pressure; HMW-Ad, high-molecular-weight adiponectin

(b) Women

	Multiple Linear Regression				Multiple Logistic Regression				
	RC	SRC	t	*p*	RC	SE	OR	95% CI	*P*
SdLDL-C	1.307	0.409	5.50	<.001	0.093	0.025	1.098	1.045–1.153	<.001
LDL-C	0.454	0.357	5.81	<.001	0.031	0.008	1.031	1.015–1.047	<.001
HDL-C	−0.337	−0.135	−3.15	<.001	−0.042	0.010	0.959	0.940–0.978	<.001
TG	−0.088	−0.114	−2.02	0.044	−0.009	0.004	0.991	0.983–0.999	0.024
FPG	0.409	0.080	1.99	0.047		---------- not selected ----------			

Variables were selected by a stepwise procedure.
MDA-LDL, malondialdehyde low-density lipoprotein; RC, regression coefficient; SRC, standardized regression coefficient; SE, standard error; OR, odds ratio; CI, confidence interval; sdLDL-C, small-dense low-density lipoprotein cholesterol calculated by Friedewald formula

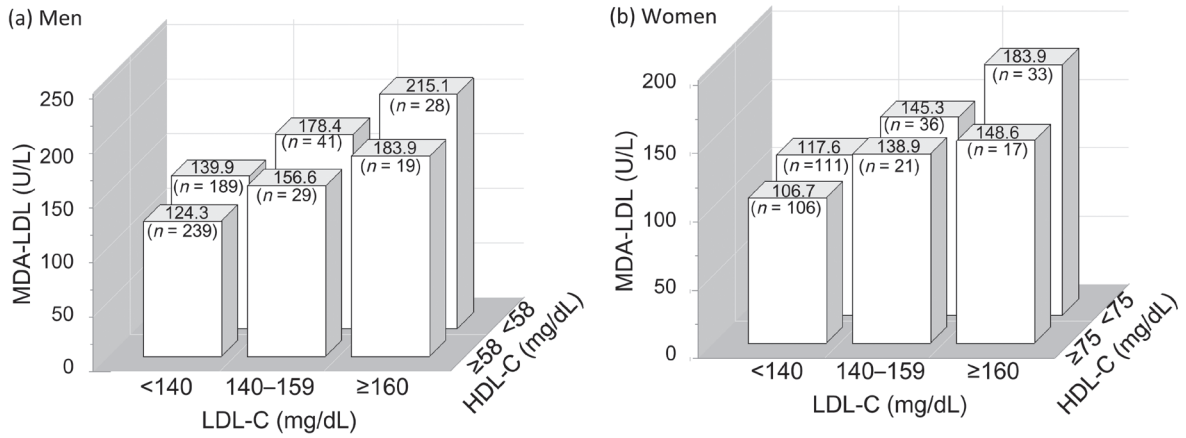

Fig. 2. Bar Graph of Mean MDA-LDL Values After Stratifying Subjects According to Sex, LDL-C and HDL-C Levels
Numbers on bars are mean values of each group (U/L). MDA-LDL, malondialdehyde low-density lipoprotein

selected for the multiple linear regression analysis, LDL-C, sdLDL-C and HDL-C were also selected for men and women in the logistic regression analysis for the upper tertile of MDA-LDL. Standardized regression coefficients in the multiple regression analysis were higher for LDL-C and sdLDL-C than for the other selected variables.

Fig. 2 is a bar graph representation of MDA-LDL levels after stratification of subjects according to gender, LDL-C levels (three groups: LDL-C of 0 to <140, 140 to <160, ≥160 mg/dL) and HDL-C levels (two groups according to median values: HDL-C of <58.0 and ≥58.0 mg/dL for men, HDL-C of <75.0 and ≥75.0 mg/dL for women). Numbers on the bars are the mean values of each group. MDA-LDL levels increased as LDL-C levels increased and HDL-C levels decreased for both men and women.

Discussion

In this study, we demonstrated that in Japanese subjects without diabetes, increases in the LDL-C level and insulin resistance may lead to an increase in the sdLDL-C level, and increases in the LDL-C and sdLDL-C levels may lead to an increase in the MDA-LDL level. SdLDL-

C levels were strongly associated with LDL-C and TG, whereas MDA-LDL levels were strongly associated with LDL-C, sdLDL-C and HDL-C levels. Therefore, we concluded that sdLDL-C is a useful lipid marker of insulin resistance in Japanese subjects with a BMI <30 kg/m^2 who are not diabetic.

Our study subject selection process was designed in consideration of the following. First, essentially all patients with type 2 diabetes mellitus are insulin resistant, and therefore, it would be difficult to assess the effect of this abnormality on the risk of CHD in this population. Moreover, HOMA-IR is not a reliable marker of insulin resistance in subjects with type 2 diabetes mellitus because of the low level of insulin secretion. Second, obesity promotes insulin resistance and is associated with increased risks of developing MetS, type 2 diabetes mellitus, and CHD[26,32], and consequently leading to increased risk of premature death and all-cause mortality. We excluded subjects with a BMI ≥ 30 kg/m^2 because of the small size of this population among Japanese[33]. Obesity, type 2 diabetes mellitus, and insulin resistance are associated with an altered lipoprotein particle profile, which might influence the risks of CHD and type 2 diabetes mellitus risk[34,35]. The particle sizes of lipoproteins, particularly sdLDL, HDL, and large very low density lipoprotein, are associated with increased risks of atherosclerosis and premature CHD[34,36,37]. On the other hand, the majority of insulin resistant subjects do not develop type 2 diabetes mellitus but remain at increased risk of CHD, regardless of whether frank hyperglycemia ensues. However, not all obese subjects are subject to an increased cardiometabolic risk and a subset of individuals who remain metabolically healthy despite having excess body fat has been described[38,39]. Unlike the metabolically unhealthy obese phenotype, metabolically healthy obesity is characterized by favorable lipid and inflammatory profiles, preserved insulin sensitivity, and a normal blood pressure[40–42]. A recent study indicated that metabolically healthy subjects displayed favorable lipoprotein particle profiles, irrespective of BMI and metabolic health definition[43], and surprisingly, higher TC and LDL-C levels were observed in both metabolically healthy obese and metabolically healthy non obese individuals[43]. On the other hand, >20% of a normal-weight population was found to be metabolically unhealthy[29]. Consistent with these observations, we found that the sdLDL-C and MDA-LDL levels were correlated positively with insulin resistance in Japanese with a BMI <30 kg/m^2 who were not diabetic.

In agreement with an earlier study[44], we demonstrated that the LDL-C level was the most significant determinant of sdLDL-C levels in Japanese subjects. However, the presence of MetS was previously found to affect both LDL-C and sdLDL-C levels, regardless of the glycemic state[44], which contradicts our finding that LDL-C levels did not significantly differ according to HOMA-IR levels. This discrepancy is likely attributable to differences in the characteristics of study subjects; more than half of the subjects of the earlier study were patients with diabetes mellitus and MetS[44], and notably, both conditions affect insulin resistance. Unfortunately, information regarding the use of diabetes and blood pressure treatments was not available. Another previous study indicated that TG and HDL-C levels affected LDL particle size in a small number of healthy Japanese males[45].

MetS is associated with insulin resistance, but an increased number of LDL particles is not part of the definition of MetS. It is of note that both sdLDL-C and MDA-LDL levels increased as HOMA-IR increased, while LDL-C levels showed no consistent increase with increasing HOMA-IR when subjects were stratified by HOMA-IR. Therefore, subjects with high insulin resistance but low LDL-C levels might be prone to developing atherosclerosis due to high levels of sdLDL-C and MDA-LDL.

MDA-LDL is considered a major form of oxidized LDL; however, the origin of this particle is not well understood[29]. Modified LDL, including oxidized LDL, is taken up by scavenger receptors, which do not bind native LDL. Scavenger receptor-mediated uptake of oxidized LDL induces foam cell formation *in vitro*, which would lead to the development of atherosclerotic lesions[43]. It is generally believed that oxidized LDL is abundant in artery wall plaque, so circulating oxidized LDL may only represent a small fraction of the total amount. This might explain why transient increases in blood levels of oxidized LDL are observed after a coronary event[43]. Despite these considerations, several studies have suggested the possibility of using circulating oxidized LDL measurements for the prediction of future cardiovascular events[29] and our results possibly support these suggestions because we found that circulating MDA-LDL levels were positively correlated with sdLDL levels.

The relationship between sdLDL-C and MDA-LDL in non-diabetes subjects is not well understood. One study found a strong association of circulating MDA-LDL with sdLDL-C in non-medicated Japanese men[25] but did not study the factors that affected sdLDL-C and MDA-LDL levels. Our study indicated that LDL-C was an important determinant of both sdLDL-C and MDA-LDL levels. However, items related to visceral fat accumulation, such as TG, HWM-Ad, and FPG, were important determinants of sdLDL-C levels. On the other hand, these items appeared to be unimportant to MDA-LDL levels, although not only LDL-C levels but also sdLDL-C levels were a major determinant of MDA-LDL levels. Thus, sdLDL might be a predominant substrate for oxidation, with consequent elevation of MDA-LDL levels as sdLDL-C levels increase.

The limitations of our study include its cross-sectional

nature, which prevented the establishment of a causal relationship. Also, the associations of insulin resistance with sdLDL-C and MDA-LDL levels might have been confounded by factors such as diet, alcohol consumption, and exercise and the effect of visceral fat mass on insulin resistance was not determined. In addition, information regarding mutations in lipid-related genes, which might also have confounded these relationships, was not available. The subjects of this study were middle-aged Japanese individuals, and it is possible that the relationships of insulin resistance with sdLDL-C and MDA-LDL levels are affected by age and ethnicity. Furthermore, detailed information regarding hypertension and dyslipidemia treatments was not available in this study. Finally, our results were calculated using data from only a fraction of the subjects who underwent annual health check-ups and, therefore, might not be applicable to the general Japanese population.

In conclusion, our data suggest close associations of the sdLDL-C level with the LDL-C level and insulin resistance, and of the MDA-LDL level with LDL-C and sdLDL-C levels in non-diabetic Japanese subjects.

Conflict of Interest

There are no conflicts of interest to declare.

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Original Article

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Evaluation of Positron Emission Tomography/Computed Tomography as Screening Modality for Advanced Colorectal Neoplasms

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Abstract

Objective: To evaluate the usefulness of ^{18}F-fluorodeoxyglucose (^{18}FDG) positron emission tomography/computed tomography (PET/CT) in identifying advanced colorectal neoplasms (ACNs) in asymptomatic individuals.

Methods: The authors retrospectively searched databases for 495 consecutive subjects who had undergone PET/CT and colonoscopy for cancer screening between August 2012 and March 2016 and their records were reviewed, including those for fecal occult blood tests (FOBT). The maximum standardized uptake value (SUVmax) was determined and receiver operating characteristics analysis was performed to identify the SUVmax with a high probability of diagnosing ACN.

Results: Eleven subjects had 12 foci with focal colorectal uptake of ^{18}FDG. Among the 12 foci, 8 were determined to be ACNs and 4 were found to be non-advanced lesions. Seven abnormalities were missed by PET/CT: four laterally spreading tumors (LSTs) and three advanced neoplasms that were 10 mm or smaller in diameter. The detection rate, sensitivity, specificity, positive predictive value, negative predictive value and accuracy for the detection of ACNs by PET/CT were 1.2%, 50%, 99%, 64%, 99%, 98%, respectively. When the optimal cut-off value was 7.3, the sensitivity and specificity were 87 and 100%, respectively. The combination of PET/CT with FOBT increased the detection rate to 2.2% and the sensitivity to 79%.

Conclusions: The present study suggests that PET/CT could identify ACNs in asymptomatic individuals with 7.3 as the optimal cut-off value of SUVmax, but it might fail to detect LSTs as well as small advanced neoplasms.

Keywords positron emission tomography, colonoscopy, fecal occult blood test, advanced colorectal neoplasms

^{18}F-fluorodeoxyglucose (^{18}FDG) positron emission tomography/computed tomography (PET/CT) is now recognized as a powerful evaluation modality for the diagnosis and staging of tumors, including colorectal cancer (CRC)[1], and the monitoring of therapy for them. Nakajo *et al.*[2] reported PET/CT to be sensitive (71%) for the detection of colonic high-grade dysplasia or early-carcinoma among 6,968 patients. On the other hand, immunochemical fecal occult blood tests (FOBT) have been widely used as a CRC screening tool and their sensitivity for identifying advanced colorectal neoplasms (ACNs) has been found to be 43.7%[3]. Luboldt *et al.*[4] found that the maximum standardized uptake value (SUVmax), the ratio of uptake in a region of interest to average whole body uptake, was 5 or more for all ACNs among 84 patients and PET/CT provided promising accuracy for their detection. Na *et al.*[5] reported that they had established an optimal cut-off value of 5.8 for diagnosing ACNs among 306 patients. In addition, dual-time-point imaging by PET/CT was considered to be possibly useful for differentiating malignant from benign, and reducing false positives in a pancreatic cancer[6] and CRC[7]. However, only a few studies have evaluated the sensitivity of PET/CT and the cut-off value of the SUVmax in screening for ACNs in asymptomatic individuals among the general population.

The present study focused on ACNs, including advanced adenomas, which are thought to be high-risk precancerous lesions[8]. Our aims were to evaluate the

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detection rate and the sensitivity of PET/CT for identifying ACNs in asymptomatic individuals and to assess whether the combination of PET/CT with other screening examinations, such as FOBT, could improve the detection rate for ACNs.

Methods

Subjects

The electronic ^{18}FDG PET/CT and colonoscopy databases were retrospectively searched for 495 consecutive subjects who had undergone PET/CT and colonoscopy as a health check-up examination at our hospital between August 2012 and March 2016.

The following data were retrieved from their medical records: demographics, results of PET/CT, endoscopic findings (type, size, and location of polyps) histological results, serum carcinoembryonic antigen (CEA), and 1-time immunochemical FOBT. The colon was divided into six segments in the PET/CT images and colonoscopic findings: cecum; ascending, transverse, descending and sigmoid colons; and rectum. Polyp type was classified according to the Paris endoscopic classification criteria[9]. An ACN was defined as presence of a cancer or an adenoma, which was 10 mm or larger in diameter, or histological evidence of high-grade dysplasia.

The Institutional Review Board approved this retrospective study and the requirement to obtain informed consent was waived (IRB No. 20150339).

PET/CT protocol

PET/CT was performed at Keio University Hospital using a Biograph mCT system (Siemens Medical Solutions, Knoxville, TN, USA). All subjects fasted for at least 6 hours before examination and the serum blood glucose level was measured before injection of ^{18}FDG at 3.7 MBq/kg. All subjects underwent scanning at 1 hour, 6 subjects at 2 hours thereafter as the delayed-phase, and data were transferred to an AZE workstation (AZE Ltd, Tokyo, Japan). Low-dose CT was performed for the whole body, followed by a three-dimensional PET emission scan which was acquired for 2 minutes per bed position. At 2 hours after FDG injection, a conventional delayed emission scan was obtained for the whole abdomen with the same scan time per bed position, after repositioning and additional CT scanning. All PET/CT images were subjected to visual and semi-quantitative analyses by radiologists who were specialized in nuclear medicine and who were blinded to the histological findings. A region was defined as PET/CT- positive if it were identified to have an abnormal focal ^{18}FDG uptake in the colon or rectum in the early-phase scanning. Otherwise, a region was defined as being PET/CT-negative. The SUVmax of PET/CT positive regions was determined in the early-phases and delayed-phases.

Interpretation of PET/CT findings and colonoscopy/histology results

The PET/CT findings and colonoscopy/histology results were classified into four categories as follows: true-positive (TP) defined as a histologically confirmed ACN in the same colonic segment as a PET/CT- positive region; false-positive (FP) defined as a PET/CT-positive region for which an ACN was not determined in the corresponding segment; true-negative (TN) defined as a PET/CT-negative region in which an ACN was not detected in colonoscopy and false-negative (FN) defined as detection of an ACN by colonoscopy in a PET/CT-negative region.

Statistical Analysis

Sensitivity, specificity, positive predictive value, negative predictive value and accuracy were calculated. Statistical difference between the TP and FP groups were determined using the Mann-Whitney U test. The optical cut-off value for differentiating the TP group from the FP group was decided such that it minimized the distance between the curve and the upper left corner. The area under the receiver operating characteristic (AUROC) curve was calculated in the receiver operating characteristic (ROC) analysis. All statistical analyses were performed using SPSS software program (SPSS version 21; SPSS, Inc, New York, NY, USA). Mean values were expressed with SD. A p value less than 0.05 was considered as statistical significance.

Results

Subjects

The 495 subjects for the study included 59 who had undergone PET/CT more than once during the study period. Two subjects with incomplete colonoscopy were excluded so 493 subjects were analyzed. The examinations were conducted within three months (average 8.7 days) of each other. Three hundred sixty-three subjects were male (74%) and 130 subjects were female (26%), and the mean age was 58.5 (range, 29–88) years old (**Fig. 1**).

Overall results for detection of ACN by PET/CT

The numbers of TP, FP, FN, and TN were 7, 4, 7, and 475, respectively (**Table 1**). Accordingly, the sensitivity, specificity, positive predictive value, negative predictive value, and accuracy were 50%, 99%, 64%, 99%, and 98%, respectively The detection rate for ACNs by PET/CT was 1.4% (7/493).

Comparison of SUVmax between TP group and FP group, and results of ROC analysis

As shown in **Table 2**, the TP group included 7 subjects with 7 cancers and 1 adenoma, whereas the FP group included 4 subjects who had no remarkable findings. The mean SUVmax for the early-phase was significantly higher for ACNs than for non-advanced lesions

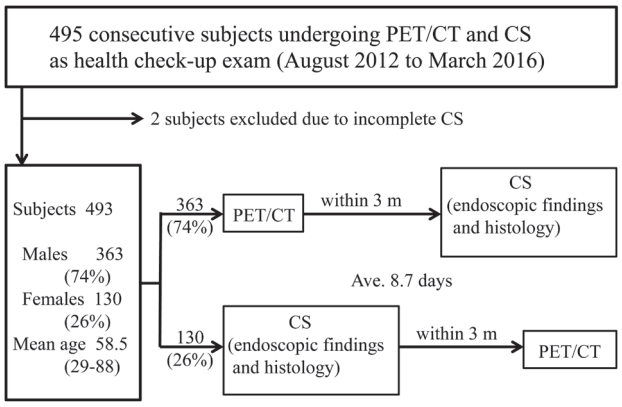

Fig. 1. Flowchart of Study

PET/CT: positron emission tomography/ computed tomography, CS: colonoscopy.

Table 1. Summarized Findings for Detection of Advanced Colorectal Neoplasms by PET/CT

Total 493	CS/histology results	
	Advanced Neoplasms	Non-Advanced Lesions
PET/CT-positive	7	4
PET/CT-negative	7	475

PET/CT: positron emission tomography/computed tomography, CS: colonoscopy

Table 2. Results for Colorectal Lesions by PET/CT and Other Screening Exams, According to TP, FN and FP

	age	sex	histology	portion	morphology	depth	size	SUVmax (early/delay)	CEA	FOBT
TP	62	M	Ca	T	Ip	m	5	4.62 / N/A	N/A	±
	59	F	Ca	C	LST-G	m	35	11.32 / 16.21	2.7	N/A
	80	M	Ca	S	Ip	m	20	8.58 / 9.13	N/A	+
	63	F	Ca	C	Is	sm3	30	9.83 / N/A	1.3	N/A
	73	M	Ca	R	Type2	ss	35	15.72 / 19.47	16.3	3+
	*69	M	Ca	R	Type2	ss	50	20.43 / 14.31	36.1	3+
				T	Type2	ss	50	8.52 / 10.31		
	57	M	Ad (sev)	R	Isp		12	12.46 / 13.68	N/A	–
FN	63	F	Ca	C	LST-G	m	40		N/A	+
	56	F	Ca	S	LST-NG (flat)	m	18		N/A	+
	55	F	Ca	S	Ip	m	10		N/A	–
	63	M	Ca	R	LST-G (mix)	sm1	40		1.1	±
	64	M	Ad (mod)	C	LST-NG (flat)		35		0.6	+
	56	M	Ad (sev)	S	IIa		2		N/A	–
	83	M	Ad	A	IIa		10		1.2	–
FP	60	F	Normal colon	R				5.18 / N/A	N/A	–
	57	M		S				5.22 / N/A	N/A	–
	64	F		A				6.20 / N/A	1.2	–
	52	F		S				3.94 / N/A	N/A	–

PET/CT: positron emission tomography/computed tomography, SUVmax: maximum standardized uptake value, CEA: carcinoembryonic antigen, FOBT: fecal occult blood test, M: male, F: female, Ca: cancer, Ad: adenoma, mod: moderate, sev: severe, LST: laterally spreading tumor, G: granular, NG: non-granular, m: intramucosal, sm: submucosal, ss: subserous.
C: cecum, A: ascending, T: transverse, D: descending, S: sigmoid, R: rectum, N/A: not applied. *69 year-old male in TP group had double cancers.

(11.4±4.9 vs 5.1±0.9, $p = 0.031$). In this study, PET/CT was performed at 2 time points only in 6 subjects with ACNs, when the mean SUVmax for the delayed-phase was 13.8±3.8. Regarding these subjects, excepting one with colon cancer having the highest SUVmax in the early-phase, all had an increased SUVmax in the delayed-phase. In the ROC analysis, when the cut-off value of the SUVmax was set at 7.3 to differentiate TP findings, the sensitivity and specificity were 87 and 100%, respectively (**Fig. 2**).

Results for colorectal lesions by PET/CT and other screening examinations, according to TP, FP, and FN

Two subjects in the TP group had advanced cancers at a resectable stage and one of them had double cancers, whereas all of 4 cancers in the FN group were early cancers, which could be completely resolved by endoscopic resection. Lesions in the FN group included four laterally spreading tumors (LSTs) (one submucosal cancer, two intramucosal cancers, and one adenoma) and 3 advanced neoplasms, which were 10 mm or smaller in diameter (one intramucosal cancer and two adenomas).

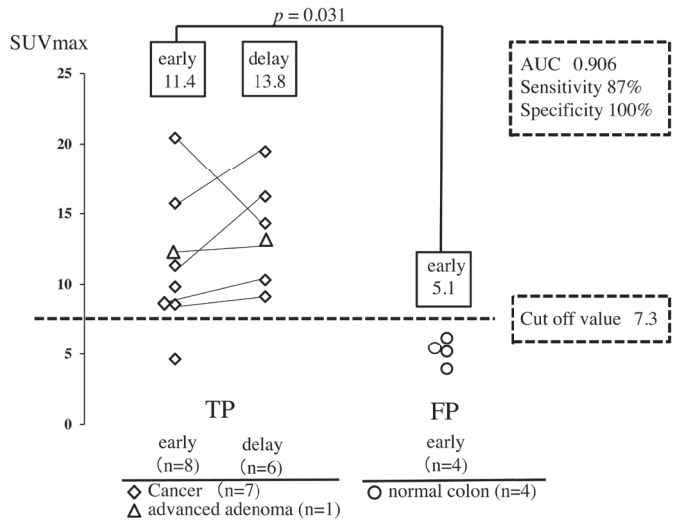

Fig. 2. Comparison of SUVmax between TP and FP Groups, and Results of ROC analysis

SUVmax: maximum standardized uptake value, AUROC: area under receiver operating characteristics (ROC) curve.

Table 3. Studies on Health Check-up Screening for Detection of Advanced Colorectal Neoplasms by PET/CT and CS

Country Authors Year	Total No. of Subjects	CS		PET/CT				
		No. of subjects No. of Advanced Neoplasms No. of Cancers	Detection rate of Advanced Neoplasms Detection rate of Cancers	Sensitivity	PPV	Accuracy	Specificity	NPV
Taiwan Huang[10] 2013	1109	36 38 5	 3.2 0.5	 15.8 60.0	 99.1 99.1	 37.5 23.1	 97.1 99.8	 96.2 98.9
Korea Hwang[12] 2015	614	10 *17 2	 1.6 0.3	 5.6	 96.8	 37.0	 75.1	 73.6
Japan Sekiguchi[11] 2016	7505	262 291 24	 3.5 0.3	 16.9 62.5	 99.3	 13.5	 99.4	
Present Study	493	14 15 11	 2.8 2.0	 50 60	 99 98	 64 60	 99 99	 98 98

PET/CT: positron emission tomography/computed tomography, CS: colonoscopy, PPV: positive predictive value, NPV: negative predictive value
* including 14 tubular adenomas with low grade dysplasia

Two subjects with advanced cancers had high serum CEA levels. A positive FOBT including (±) was noted for 4 subjects with cancer in the TP group, and for 3 of 4 subjects with cancer in the FN group, whereas all 4 subjects in the TN group had a negative FOBT.

Discussion

Only three studies have evaluated the sensitivity of PET/CT for the detection of ACN as a screening modality, as shown in **Table 3**. The results of the Taiwanese study[10] conducted in 2013 and Japanese study in 2016[11], which included the largest number of screened individuals, were quite similar: detection rates for cancers and ACNs were 0.3–0.5% and 3.2–3.5%, respectively, and the sensitivities of PET/CT for cancers and ACNs were 60.0–62.5% and 15.8–16.9, respectively. The Korean study[12] performed in 2015 had only 3 ACNs, which included 2 cancers, resulting in very low sensitivity for detection of ACNs by PET/CT; the findings actually included 14 tubular adenomas with low grade dysplasia as ACNs. On the other hand, the present study had a much higher detection rate for cancers (2.0%) and the sensitivity of PET/CT for ACNs was the highest (50%). These differences are mainly due to the fact that our study population had a higher percentage of cancers and a lower percentage of advanced adenomas than the study conducted in Taiwan and the Japanese study. Another reason would be that it is easier for PET/CT to detect more advanced histological grade neoplasms[13]. Thus, as there have been very few studies on the clinical usefulness of PET/CT for detecting ACNs in asymptomatic average-risk screenees, more

are needed, not only from East Asia but also Western countries.

Comparing ACNs that were PET/CT-positive to those that were PET/CT negative, most of the former were more than 10 mm in size. This result seems to be in accordance with that of previous studies in which the detection rate by PET/CT was positively correlated with the size of ACN[13,14]. Kaku, *et al.*[15] reported that LSTs accounted for 17.2% of ACNs found in a large average-risk population undergoing screening colonoscopy. Interestingly, the authors detected 5 LSTs, 4 of them intramucosal cancers (18–40mm in diameter), by colonoscopy, but only one (35 mm size in diameter) of these LSTs could be found by PET/CT alone. These findings should be carefully taken into consideration in the interpretation of PET/CT images, as an LST, a flat lesion, might be missed by PET/CT, even though it is sufficiently large in size.

SUVmax is a semi-quantitative measurement that has come into widespread use in the differentiation of malignant from benign neoplasms on PET/CT[6], although a high SUVmax may also be found for various benign conditions evaluated using this modality[16] because ^{18}FDG is not a neoplasm-specific substance. Comparing the TP group and the FP group, the mean age of subjects in the former (66.1 years old) was higher than that in the latter (58.3 years old). Also, our data clearly indicate that SUVmax in the TP group was significantly higher than in the FP group. Additionally, the optimal cut-off value of SUVmax (7.3) for differentiating ACNs from non-advanced lesions in asymptomatic individuals was similar to that calculated by Sekiguchi, *et al.* (6.3)[11].

Previously, sensitivities of the FOBT were seen to range from 22 to 44% for ACNs and from 56 to 92% for CRCs[3,17,18]. More recently, a nationwide Japanese survey reported that the sensitivity of FDG-PET for CRC (86.0%) was higher than that of 2-time FOBT, whereas the sensitivity of FDG-PET for CRC and adenoma together (63.7%) was lower than that of 2-time FOBT[19]. Positive FOBTs including (±) were noted in 4 (3 cancers and 1 advanced adenoma) of 7 subjects in the FN group. Therefore, the combination of PET/CT with FOBT could increase the detection rate from 1.4% to 2.2% and the sensitivity from 50% to 79%, as the findings of the Japanese survey[19] suggested that these two methods could be complementary. Furthermore, FOBT is more sensitive for cancer in the distal colon than in the proximal colon, whereas PET/CT has high sensitivity regardless of the cancer location. Although PET/CT has the major problems of high cost and radiation exposure, combining it with the FOBT would contribute to the detection of ACNs in asymptomatic average-risk subjects in opportunistic screening in the clinical setting.

The present study has some limitations. First, it had a relatively small number of samples, which were obtained from a single tertiary referral hospital. Second, some studies have demonstrated that the use of delayed PET/CT led to a reduction in the number of false-positive findings and increased the accuracy in the detection of cancer[20,21] but the authors were unable to evaluate the diagnostic ability of dual-time point PET/CT because it is not routinely conducted. Finally, we may have missed some colonic neoplasms in colonoscopy, which is considered to be the gold standard.

Conclusions

The present study suggests that PET/CT could identify ACNs in asymptomatic individuals with 7.3 as the cut-off value for SUVmax, but LSTs and small ACNs might not be detected.

Conflicts of Interest

All authors report that they have no disclosures relevant to this publication.

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Case Report

Ningen Dock International 2017 ; 4 : 95–97

A Case Report of Follicular Lymphoma Incidentally Detected in Ningen Dock Using Positron-emission Tomography

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Abstract

Hematological malignancies have seldom been mentioned as a target of Ningen Dock. Positron-emission tomography (PET) using 18-fluoro-deoxyglucose is known to be highly sensitive in detecting various kinds of malignancies and has increasingly been added to Ningen Dock examinations. We describe the clinical course of a 59-year-old woman who was incidentally diagnosed with follicular lymphoma using PET in a routine health check-up exam. She was treated with 6 cycles of immunochemotherapy, resulting in complete remission. During an observation period of 93 months from presentation, there was no relapse.

Although the efficacy of PET in cancer screening is widely established, the frequency that malignant lymphoma is detected in PET is lower than for other common cancers. Malignant lymphoma is the major type of hematological tumor. PET-based screening has certain problems, one of them cost-effectiveness. It may also lead to overtreatment of low-grade lymphoma and produce false negative results. However, if lymphoma is suspected from the findings, an immediate histological diagnosis is needed to determine the treatment policy.

Keywords positron emission tomography, routine health check-up, lymphoma

In Japan, Ningen Dock, a series of systematic routine medical exams undergone on a voluntary basis, has played a major great role in disease prophylaxis and health promotion. Its potential to detect various malignancies has also been recognized. However, hematological malignancies, the major one malignant lymphoma (ML), have seldom been mentioned as a target of Ningen Dock.

Positron-emission tomography (PET) using 18-fluoro-deoxyglucose (FDG) is a sensitive modality that can be used to screen for or monitor various kinds of malignancies[1]. Its usefulness as a screening exam for cancer has led to a marked increase in institutions that have added PET to their Ningen Dock[2]. We describe a patient with follicular lymphoma (FL), an indolent type of lymphoma, which was incidentally diagnosed using PET in a routine health check-up. To our knowledge, there has been no detailed report of such a case before.

We took adequate care to ensure the privacy of the patient, which included concealing her name, date of birth and the time of consultation.

Case report

A 59-year-old woman visited our department because of abnormal findings in PET. She had annually undergone PET as a routine medical check-up exam for several years and there was no particular medical history. Abnormal FDG uptake was seen in her pharynx, mediastinum, peritoneal cavity and inguinal regions, with a maximum standardized uptake value of 6.2 (**Fig. 1**). She had no subjective symptoms such as fever elevation, body weight loss or sweating. Physical examination revealed right inguinal tumors of 3 cm in diameter. A biopsied specimen from the inguinal lymph node was pathologically evaluated and the diagnosis of FL, grade I was made (**Fig. 2**). Immunohistochemistry showed positivity for CD20 and BCL2. Chromosomal analysis of the tumor cells revealed translocation of chromosome 14 and 18. Bone marrow was not involved. Her clinical stage was determined as IIIA. Hemoglobin and serum lactate dehydrogenase (LDH) levels were within normal limits (14.2g/dL and 161IU/L, respectively), but elevation of serum interleukin-2 receptor (IL-2R) was noted (747U/mL, normal range less than 519) (**Table 1**). According to the Follicular Lymphoma International Prognostic Index[3] she came under the intermediate risk group. Since more than 3 of the lesions involved were larger than 3 cm in diameter, the tumor bulk was regarded as high according to previously established criteria[4]. With immunochemotherapy

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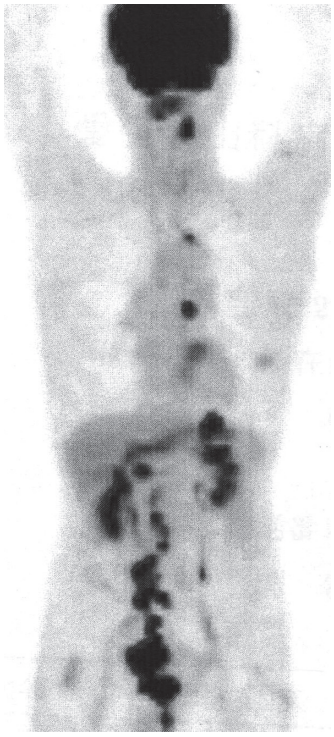

Fig. 1. PET Imaging of the Patient

Multiple lymph nodes in her neck, mediastinum and peritoneal space show abnormal uptake of FDG, with a maximum standardized uptake value of 6.2.

Table 1. Laboratory Data on Admission

WBC	8360 /μL	LDH	161 IU
Stab	1.0%	T-Bil	0.4 mg/dL
Segment	64.0%	AST	23 IU/L
Lym	28.0%	ALT	26 IU/L
Mono	3.0%	ALP	270 IU/L
Eo	3.0%	T-cho	141 mg/dL
Baso	1.0%	CRP	0.38 mg/dL
		BUN	9.3 mg/dL
RBC	458x10^4 /μL	Cr	0.50 mg/d
Hb	14.2 g/dL	Na	140 mEq/L
Ht	41.0%	K	3.9 mEq/L
		Cl	104 mEq/L
PLT	26.0x10^4 /μL	BS	147 mg/dL
		HbA1c	6.5%
		IL-2R	747 U/mL

Abnormal values are underlined.

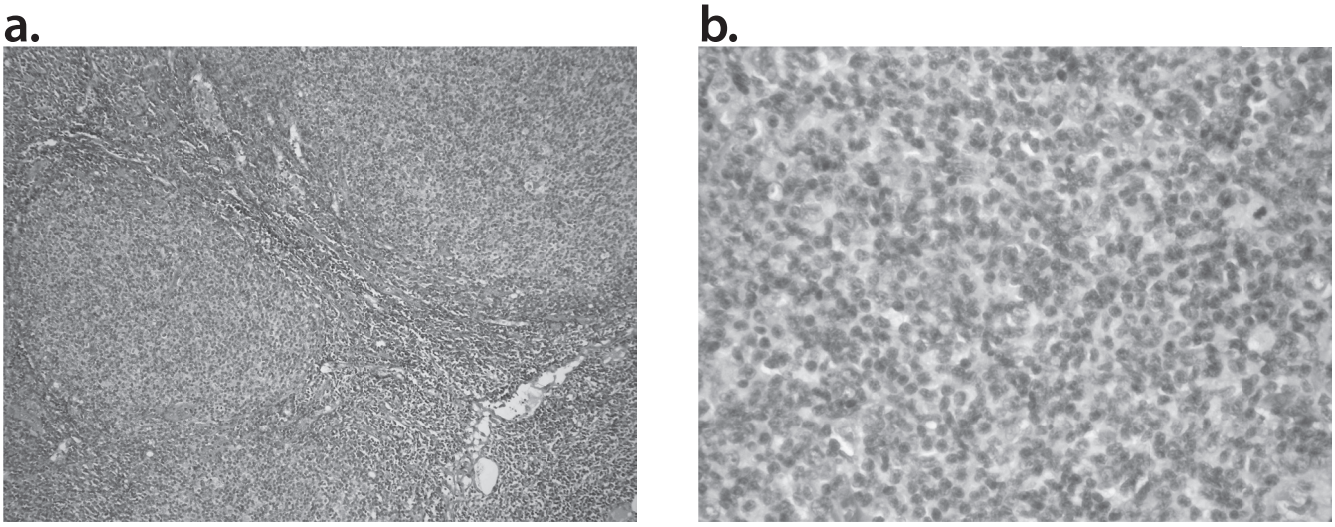

Fig. 2. Pathological Findings of Biopsied Specimen From Inguinal Lymph Node

a. Enlarged follicles can be observed (x100 magnification).
b. Monotonous proliferation of atypical cells without macrophage or centroblast-like large-size cells, indicating grade 1 (x400 magnification).

consisting of rituximab, cyclophosphamide, adriamycin, vincristine and prednisolone, complete remission was achieved. During an observation period of 93 months from presentation, there were no particular events.

Discussion

Although it has the problem of substantial cost[5], PET is recognized as a screening modality with high sensitivity for various kinds of cancer, i. e. lung[6], breast[7], and colon cancer[8]. It is notable that PET has often detected these cancers in the earlier stages[2,5] and since a considerable number of them were reported to be curable with surgical treatment[2,5], its effectiveness as a means of cancer screening has been widely established.

The significance of screening for hematological malignancies using PET has seldom been evaluated probably because of their rarity in the general population. Previous detailed analyses by Chen *et al*[1]., Minamimoto *et al.*[2] and Kawada *et al.*[9] assessed the frequency of incidental detection of ML by PET as 0.08% (3 among 3,631), 0.02% (38 among 165,853) and 0.07% (7 among 10,292), respectively. This is quite low compared with other common types of malignancy (incidental detection rates of 2.48%, 0.18% and 3.10% for lung cancer and 2.48%, 2.32% and 2.23% for colon cancer in the above 3 studies, respectively[1,2,9]). However, a much higher frequency for ML was reported by Kamiyama *et al.* (18 among 10659, 0.17%)[10]. On the other hand, the above detection rates for lung and colon cancer seem high compared with the morbidity rates in the general population reported by Japanese National Cancer Center (NCC)[11]. In 2012, NCC morbidity rates for lung and colon cancer and ML were 0.0124%, 0.125% and 0.025% for males and 0.055%, 0.087% and 0.017% for females, respectively. This might be because NCC data is not only based on the results of PET screening. Therefore, the reason for this discrepancy needs to be elucidated through detailed analysis of these data.

Most patients with incidentally diagnosed lymphoma have indolent subtypes, *i. e.* FL, nodal or extranodal marginal zone lymphoma or small lymphocytic lymphoma[2,10], meaning that screening could be detecting asymptomatic patients who could live a long time without visiting hospital. In addition, these low-grade subtypes of lymphoma may not be curable, unlike early-stage lung or colon cancer. In the management of a patient with asymptomatic FL, such as in the present case, a "watch-and-wait" approach still plays an important role, even in the advanced stages, since overtreatment may be problematic[12]. This reduces the value of the early detection of FL.

An additional problem is false negative results. Two of the 4 (50%) subjects with FL in the study by Kamiyama *et al.* did not show abnormal uptake in PET[10], possibly placing a limitation on its role in screening. Also, blood glucose levels are known to reduce the sensitivity of PET because of increased background FDG uptake. Since our patient appeared to have diabetes mellitus as shown in **Table 1**, the number of involved lesions might have been underestimated. However, her blood sugar (BS) level at presentation was maintained at less than 150 mg/dL and PET was performed in the fasting condition[13]. Therefore, hyperglycemia appeared not to affect clinical staging or risk assessment.

Based on the above, although PET screening for ML may not be cost-effective, if ML is suspected from the findings, an immediate histological diagnosis is needed to determine the treatment policy.

Conflict of Interest

None of the authors has any conflict of interest.

Informed Consent

Written informed consent was acquired from the patient involved in this study.

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I sincerely thank their kind cooperation.

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The Regulations of the International Society of Ningen Dock

Article 1
Name
The name of the association shall be the International Society of Ningen Dock.

Article 2
Office
The Society has its principal office in Japan Society of Ningen Dock.

Article 3
Aims
The Society, an organization of Japan Society of Ningen Dock for international operations, aims to contribute to global health promotion by enhancing the development of ningen dock as a medical check-up system.

Article 4
Tasks
The Society conducts the following tasks to achieve the aims described in the preceding section.
1. Holds congress (World Congress on Ningen Dock), board meetings, lectures, and committee meetings
2. Publishes journals and news magazines
3. Communicates and cooperates with related academic societies both in Japan and overseas
4. Promotes research activities in ningen dock and related fields
5. Does whatever is necessary to achieve the aims of the Society

Article 5
Membership
1. The Society consists of the following members
   1) Regular member
      A regular member shall be a member of the International Society of Ningen Dock who agrees to the aims of the Society, and has expert knowledge, techniques, or experience in the areas associated with the Society.
   2) Supporting member
      A supporting member shall be a person, a corporation, or a group that agrees to the aims of the Society, and supports its programs.
   3) Honorary member
      An honorary member shall be recommended, from those who have significantly contributed to the areas associated with the Society, by the executive board.
2. Those who want to apply for regular or supporting membership of the Society shall submit the prescribed application form with the membership fee.
3. The board meeting will process applications mentioned in the preceding section, and promptly notify the applicants of its decision.

Article 6
Officials
1. The Society shall appoint the following honorary advisors and officials.

Honorary advisor: Number not decided
Congress president: 1
President: 1
Vice president: 3 (from Japan : 2, overseas: 1)
Board members: up to 25 (from Japan : 15 or less, overseas : 10 or less)
Auditor: 2

Article 7
Honorary advisor
1. An honorary advisor shall be appointed by the president from those who have contributed to the development of the Society for a long period, and approved by the executive board.
2. Honorary advisors shall be eligible to attend the board meeting, and to express opinions; honorary advisors will not have voting rights.

Article 8
Congress president
1. The congress president shall be recommended by the executive board and appointed by the president.
2. The congress president shall represent the Society and host the World Congress on Ningen Dock as a scientific meeting.

Article 9
President
1. The president shall be selected by and from among board members and delegated by the president of Japan Society of Ningen Dock.
2. The president shall preside the Society.

Article 10
Vice president
1. The vice president shall be appointed, from among board members, by the president.
2. The vice president shall assist the president. In the case of accident, one of the vice presidents will be appointed by the president and will temporarily take over the duties.

Article 11
Board members
1. Board members from Japan shall be selected among candidates from regular members at Japan Society of Ningen Dock.
2. Overseas board members shall be selected at the recommendation of the executive board.
3. Board members execute duties for the Society under the orders from the president.
4. Board members, together with the president and the vice president, comprise the executive board.

Article 12
Board meeting
1. The president will call a board meeting on an as-needed basis, and serves as the chairman of the meeting.
2. The board meeting will pass resolutions on important matters of the Society.
3. The board meeting shall have the right to start proceedings if the majority of all the board members (including a letter of proxy) attend the meeting.
4. The board meeting shall pass resolutions with the majority votes of attendances.

Article 13
Auditor
Auditors shall audit accounts of the Society, and report to the board meeting.

Article 14
Commissioner
For the aims of successful programs of the Society, the president will set up committees and divisions through the resolutions of the executive board, and delegate the commissioners to regular members or other members of the Society.

Article 15
Accounting
1. The fiscal year for the Society starts on April 1 every year and ends on March 31 the following year.
2. Expenses required for the Society shall be covered by the following revenues.
   1) Membership fees
   2) Grants
   3) Donations
   4) Others

Article 16
Modification of rules
The rules of the Society can be amended by the resolution of the executive board.

Article 17
Miscellaneous provisions
Detailed regulations necessary for the enforcement of the rules of the Society are defined elsewhere by the president with the approval of the executive board.

Article 18
Additional clause
The Regulations of the International Society of Ningen Dock will come into effect on September 15, 2006.

Detailed Regulations of the International Society of Ningen Dock

Detailed regulations of the International Society of Ningen Dock are defined as follows:

(Detailed regulations on members)

Article 1

1. Members shall pay the following annual membership fee; honorary members will be exempt from membership fee.
   1) Regular member : 2,000 yen
   2) Supporting member : from one unit (unit: 20,000 yen)
2. Annual membership fee paid shall not be refunded for any reason.
3. Members with foreign citizenship shall pay a 3-year membership fee of 50 dollars.

Article 2

Members will be given priority in the following events :

1) Participation in scientific meetings hosted by the Society;
2) Contributions of articles to and receipt of the journal of the Society.

Article 3

Members shall lose their memberships in the event of the following:

1) Withdrawal from membership;
2) Adjudication of incompetence or quasi-incompetence;
3) Death or adjudication of disappearance, or dissolution of the group in the case of a member of a supporting group;
4) Delinquency in payment of membership fee for over three year.

Article 4

Those intending to withdraw from the Society must submit the notice of withdrawal in the prescribed form to be approved by the executive board.

Article 5

The Society can expel a member to whom either of the following would apply, with a resolution of the executive board:

1) Those who violate their duty as members of the Society;
2) Those who damage the honor of members of the Society or act against the aims of the Society.

Article 6

Those who satisfy Sections 1 and 2 of Article 5 of the Regulations of the International Society of Ningen Dock will be accepted as members of the Society.

(Detailed regulations on officials)

Article 7

1. The president will be selected from the board members of Japan Society of Ningen Dock.
2. In principle, the majority of board members from Japan will be selected from among the board members of Japan Society of Ningen Dock.

3. Overseas board members will essentially be selected from Asia, Pacific Rim, North America, or Europe.

Article 8

1. The term of the congress president will be from the end of the congress of which he/she is in charge to the next congress.
2. The term of board members will be six years (two terms of three years).

(Detailed regulations on congress and board meeting)

Article 9

Congress and board meeting will be held as follows :

1) The title of the congress will be World Congress on Ningen Dock.
2) In principle, the congress and the board meeting will be held once every three years; with the resolution of the executive board, however, the congress and the board meeting will be held as needed.
3) The congress and the board meeting will be held at the same time.
4) The name of the congress president and the location of the next congress will be announced.

Article 10

1. Those who want to take part in the congress shall pay the participation fee, which is defined separately.
2. Participation fee for the congress will be defined accordingly by the congress president.
3. Only regular members shall be allowed to present the results of their studies, except those who have been approved by the congress president.

(Enforcement of the detailed regulations)

Article 11

1. The detailed regulations will come into effect on September 15, 2006.

INSTRUCTIONS TO AUTHORS

Ningen Dock International
Official Journal of Japan Society of Ningen Dock

Ningen Dock is the official journal of Japan Society of Ningen Dock, in which original articles, case reports, and review articles in both Japanese and English are published. Ningen Dock accepts only manuscripts that are original work in the field of ningen dock and related areas not previously published or being considered for publication elsewhere, except as abstracts. The manuscripts published in Ningen Dock will appear on the website of our society.

If the manuscript concerns a clinical study, it must be in accordance with the Declaration of Helsinki of 1964 (subsequent revisions included). Therefore, for a manuscript whose content is epidemiological or clinical research, the approval of the facility's Institutional Review Board (IRB) or the Ethics Committee of Japanese Society of Ningen Dock must have been obtained for the study described. Also, in the text, it should be indicated that informed consent has been obtained from subjects. Additionally, for case reports, it should be stated that adequate care has been taken to ensure the privacy of the subject concerned.

Online submission system

Ningen Dock uses an online submission system called ScholoarOne Manuscripts.
Please access http://mc.manuscriptcentral.com/ningendock
This site is only in Japanese at this time.

Preparation of manuscript

All manuscripts must be written in English with MS-Word, Excel, PowerPoint and/or a common graphic format. Authors who are not fluent in English must seek the assistance of a colleague who is a native English speaker and is familiar with the field of the manuscript.

The title, abstract, text, acknowledgments, references, tables, and figure legends should begin on separate sheets, with pages numbered, and be typed double-spaced using the 12-point font size in MS-Word.
Files for submission should be prepared in English in a Microsoft Word or other file format that may be uploaded to the online system.

Available formats for files to be uploaded: doc (docx), xls (xlsx) ppt (pptx), jpg, tiff, gif, ai, eps, psd File names must consist of alphanumeric characters and an extension.

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All measurements should be expressed in SI units. Less common abbreviations should be spelled out at first usage and the abbreviated form used thereafter.

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Titles should be concise and informative. Include the full names of authors, names and addresses of affiliations, and name and address of a corresponding author to whom proofs are to be sent, including a fax number, telephone number and e-mail address.

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The abstract should not exceed 250 words, and should be arranged under the following subheadings: Objective, Methods, Results, Conclusions, and have up to 4 keywords.

Types of articles

Original articles: An original article should not exceed 3,000 words, and should be arranged as follows: Abstract, Objective, Methods, Results, Discussion, (Conclusion), (Acknowledgments), and References.

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References should be numbered consecutively in order of appearance in the text and cited in the text using superscript numbers. For example, according to the study by Sasamori[1)]. For journals, the names and initials of the first three authors, followed by "et al" if there are other coauthors, the complete title, abbreviated journal name according to Index Medicus, volume, beginning and end pages, and year should be included. For books, the names and initials of the first three authors, followed by "et al" if there are other coauthors, the complete title, book name, edition number, beginning and end pages, name and city of publisher, and year should be included. Examples of references are given below.

Journal: Ishizaka N, Ishizaka Y, Nagai R, et al: Association between white cell count and carotid arteriosclerosis in Japanese smokers. Atherosclerosis 2004; 175: 95-100.

Book: Kaplan NM: Measurement of blood pressure. In: Kaplan NM(ed), Kaplan's Clinical Hypertension. 7th ed., Lippincott William & Wilkins, Philadelphia, 2002, 25-55.

Tables

Tables should be cited in the text, and numbered sequentially with Arabic numerals. Each table should be given a number and a brief informative title, and should appear on a separate page. Explain in footnotes all abbreviations used.

Figures

Figures should be cited in the text, and numbered sequentially with Arabic numerals. A brief descriptive legend should be provided for each figure. Legends are part of the text, and should be appended to it on a separate page. Color figures can be reproduces if necessary, but the authors will be expected to contribute towards the cost of publication.

Conflict of Interest (COI)

All authors are required to disclose any conflict of interest (COI) on the form designated by the Japan Society of Ningen Dock.

If no author has any COI, this should be indicated in the manuscript.

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The corresponding author will receive PDF proofs, the author should correct only typesetting errors. After correcting, page proofs must be returned promptly.

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Check list for submission of papers to Ningen Dock
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- ☐ Case report (not more than 2,000 words)
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- ☐ Type double space using 12-point

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- ☐ Title of paper
- ☐ Full names of authors and affiliations without title of MD, PhD, etc
- ☐ Full name and address of a corresponding author including fax number, telephone number and e-mail address.
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Abstract:

- ☐ Not more than 250 words.
- ☐ Arranged in the order of Background, Methods, Results, and Conclusion.
- ☐ Up to four key words.

Text of paper:

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Abbreviations

1	**1,5-AG**	1,5-anhydroglucitol	61	**hCG**	human chorionic gonadotropin
2	**17-OHCS**	17α-hydroxycorticosteroid	62	**HCV**	hepatitis C virus
3	**95% CI**	95% confidence interval	63	**HDL-C**	high-density lipoprotein cholesterol
4	**α-GI**	α-glucosidase inhibitor	64	**HLA**	histocompatibility [leucocyte] antigen
5	**β_2-MG**	β_2-microglobulin	65	**HPLC**	high-performance liquid chromatography
6	**γ-GTP**	γ-glutamyl transpeptidase	66	**Ht**	hematocrit
7	**A/G ratio**	albumin-globulin ratio	67	**ICD**	International Classification of Disease
8	**ABI**	ankle-brachial index	68	**ICU**	intensive care unit
9	**ACTH**	adrenocorticotropic hormone	69	**IFG**	impaired fasting glucose
10	**ADL**	activities of daily living	70	**IGT**	impaired glucose tolerance
11	**AFP**	α-fetoprotein	71	**IMT**	intima-media thickness
12	**ALP**	alkaline phosphatase	72	**LAP**	leucine aminopeptidase
13	**ALT**	alanine aminotransferase	73	**LDH**	lactate dehydrogenase
14	**Apo (a)**	apolipoprotein (a)	74	**LDL-C**	low-density lipoprotein cholesterol
15	**APTT**	activated partial thromboplastin time	75	**Lp(a)**	lipoprotein (a)
16	**AST**	aspartate aminotransferase	76	**LPL**	lipoprotein lipase
17	**BMI**	body-mass index	77	**MCH**	mean corpuscular hemoglobin
18	**CA125**	carbohydrate antigen 125	78	**MCHC**	mean corpuscular hemoglobin concentration
19	**CA19-9**	carbohydrate antigen 19-9	79	**MCV**	mean corpuscular volume
20	**cAMP**	cyclic adenosine 3', 5'-monophosphate	80	**METs**	meatbolic equivalent
21	**CAPD**	continuous ambulatory peritoneal dialysis	81	**MetS**	metabolic syndrome
22	**CBC**	complete blood cell count	82	**MMG**	mammography
23	**Ccr**	creatinine clearance	83	**MRA**	magnetic resonance angiography
24	**cDNA**	complementary deoxyribonucleic acid	84	**MRI**	magnetic resonance imaging
25	**CEA**	carcinoembryonic antigen	85	**mRNA**	messenger RNA
26	**cGMP**	cyclic guanosine 3', 5'-monophosphate	86	**MRSA**	methicillin-resistant *Staphylococcus aureus*
27	**ChE**	cholinesterase	87	**MSW**	medical social worker
28	**CKD**	chronic kidney disease	88	**NMR**	nuclear magnetic resonance
29	**COI**	conflict of interest	89	**PET**	positron emission tomography
30	**COPD**	chronic obstructive pulmonary disease	90	**PSA**	prostate-specific antigen
31	**CK**	creatinine kinase	91	**PTH**	parathyroid hormone
32	**CRP**	c-reactive protein	92	**PWV**	pulse wave velocity
33	**CT**	computed tomography	93	**QOL**	quality of life
34	**CVA**	cerebrovascular accident	94	**RBC**	red blood cell
35	**D-Bil**	direct bilirubin	95	**RF**	rheumatoid factor
36	**DBP**	diastolic blood pressure	96	**RI**	radioactive isotope
37	**DNA**	deoxyribonucleic acid	97	**RIA**	radioimmunoassay
38	**DRG**	diagnosis-related group	98	**RNA**	ribonucleic acid
39	**dsDNA**	double stranded deoxyribonucleic acid	99	**SBP**	systolic blood pressure
40	**EBM**	evidence-based medicine	100	**SD**	standard deviation
41	**ECG**	electrocardiogram	101	**SEM**	standard error of the mean
42	**eGFR**	estimated glomerular filtration rate	102	**STD**	sexually transmitted disease
43	**EIA**	enzyme immunoassay	103	**T-Bil**	total bilirubin
44	**ELISA**	enzyme-linked immunosorbent assay	104	**T_3**	triiodothyronine
45	**EPO**	erythropoietin	105	**T_4**	thyroxine
46	**ESR**	erythrocyte sedimentation rate	106	**TC**	total cholesterol
47	**FBG**	fasting blood glucose	107	**TG**	triglyceride
48	**FDA**	Food and Drug Administration	108	**TIA**	transient (cerebral) ischemic attack
49	**FEV**	forced expiratory volume	109	**TIBC**	total iron binding capacity
50	**FEV_1**	forced expiratory volume in one second	110	**tPA**	tissue plasminogen activator
51	**FEV_1%**	forced expiratory volume % in one second	111	**TPHA**	*Treponema pallidum* hemagglutination assay
52	**FPG**	fasting plasma glucose	112	**TSH**	thyroid stimulating hormone
53	**FSH**	follicle stimulating hormone	113	**TTT**	thymol turbidity test
54	**FT3**	free triiodothyronine	114	**UCG**	ultrasonic echocardiography
55	**FT4**	free thyroxine	115	**UIBC**	unsaturated iron binding capacity
56	**FVC**	forced vital capacity	116	**UN**	urea nitrogen
57	**GFR**	glomerular filtration rate	117	**VLDL**	very-low-density lipoprotein
58	**GH**	growth hormone	118	**WBC**	white blood cell
59	**Hb**	hemoglobin	119	**WHO**	World Health Organization
60	**HbA1c**	hemoglobin A1c	120	**ZTT**	zinc sulfate (turbidity) test

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