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REVIEW ARTICLE

National Clinical Database feedback implementation for quality improvement of cancer treatment in Japan: from good to great through transparency

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Abstract The National Clinical Database (NCD) of Japan was established in April, 2010 with ten surgical subspecialty societies on the platform of the Japan Surgical Society. Registrations began in 2011 and over 4,000,000 cases from more than 4100 facilities were registered over a 3-year period. The gastroenterological section of the NCD collaborates with the American College of Surgeons' National Surgical Quality Improvement Program, which shares a similar goal of developing a standardized surgical database for surgical quality improvement, with similar variables for risk adjustment. Risk models of mortality for eight procedures; namely, esophagectomy, partial/total gastrectomy, right hemicolectomy, low anterior resection, hepatectomy, pancreaticoduodenectomy, and surgery for acute diffuse peritonitis, have been established, and feedback reports to participants will be implemented. The outcome measures of this study were 30-day mortality and operative mortality. In this review, we examine the eight risk models, compare the procedural outcomes, outline the feedback reporting, and discuss the future evolution of the NCD.

Keywords Gastrointestinal surgery · National Clinical Database · Nationwide web-based database · Mortality · Risk model

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Abbreviations

NCD	National Clinical Database
ACS NSQIP	The American College of Surgeons National Surgical Quality Improvement Program
ASA	American Society of Anesthesiologists
CNS	Central nervous system
COPD	Chronic obstructive pulmonary disease
DIC	Disseminated intravascular coagulation
JSS	The Japan Surgical Society
JSGS	The Japanese Society of Gastroenterological Surgery
ROC	Receiver operating characteristic
SIRS	Systemic inflammatory response syndrome
SSI	Surgical site infection

Introduction

Until recently, no nationwide data on cancer were available in the field of gastroenterological surgery in Japan. In 2006, the Japanese Society of Gastroenterological Surgery (JSGS) formed a committee to devise a database to track surgical patients treated in Japan over the 3 years from 2006 to 2008, and reported relatively low mortality rates for the major surgical procedures [1, 2]. The JSGS acknowledged the importance of risk-adjusted surgical outcomes for accurate comparisons and quality improvement; thus, in April, 2010, it created the database as a subset of the National Clinical Database (NCD) of Japan with major support from the Japan Surgical Society (JSS). Eight other surgical professional societies, including the Japanese Society for Cardiovascular Surgery, the Japanese Society for Vascular Surgery, the Japanese Association for Thoracic Surgery, the Japanese Association for Chest Surgery, the Japanese Society of Pediatric Surgeons, the Japanese Breast Cancer

Society, the Japan Association of Endocrine Surgeons, and the Japanese Society of Thyroid Surgery, joined the NCD. Registrations began in 2011, since when more than 4100 facilities have enrolled and over 4,000,000 cases have been registered over a 3-year period.

The gastroenterological section of the NCD collaborates with the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) [3], which shares a similar goal of developing a standardized surgical database for quality improvement. The NSQIP was originally developed in the 1990s by the United States Veterans' Health Administration and led to marked improvement in surgical quality [4]. The American College of Surgeons (ACS) initiated the ACS-NSQIP in 2006 and demonstrated improved surgical outcomes across all participating hospitals in the private sector [5]. The core members of the NCD joined the meetings and seminars of the ACS-NSQIP and debated various aspects of clinical databases, such as data collection methods and public relations [3]. In addition, the NCD implemented the same items as those of the ACS-NSQIP to conduct international cooperative studies. Reliable 30-day outcomes, including mortality and morbidity, serve as a quality improvement catalyst for ACS-NSQIP-participating institutions. Risk adjustment is a key component of the ACS-NSQIP and most variables included in risk adjustment models focus on patient factors and comorbidities. In this article, we focused on the gastrointestinal surgery subset of the NCD. All cases are input with items representing the surgical performance in each specialty for the following eight procedures: esophagectomy (Eso), total/distal gastrectomy (TG/DG), right hemicolectomy (RHC), low anterior resection (LAR), hepatectomy performed for more than one segment apart from the lateral segment (Hx), pancreaticoduodenectomy (PD), and surgery for acute diffuse peritonitis (ADP). Risk models of mortality for each procedure were created using approximately 120,000 cases registered in 2011, and each model has been accepted and published in peer-reviewed journals [6–13]. We review the results and discuss the future evolution of the NCD using these risk models in terms of the surgical quality improvement program in Japan.

NCD data entry system

Submitting cases to the NCD is a prerequisite for all member institutions of the JSS and JSGS, and only registered cases can be used for board certification [3]. To assure the traceability of data, the NCD continuously tracks persons who approve data, persons in departments who are in charge of annual cases, and persons responsible for data entry, through its web-based data management system. The NCD also continuously validates data consistency through random site visits.

The NCD variables are almost identical to those applied in the ACS-NSQIP (http://www.site.acsnsqip.org/wp-content/uploads/2013/10/ACSNSQIP.PUF_.UserGuide.2012.pdf#search='user+guide+for+the+2012+ACS+NSQIP). The potential independent variables include patient demographics, pre-existing comorbidities, preoperative laboratory values, and perioperative data. The demographic variables include age, sex, smoking status, and drinking status. Patients were categorized according to whether they were brought to hospital directly, by ambulance. General factors such as the patient's body mass index (BMI) and preoperative functional status, defined as independent, partially dependent, or totally dependent, according to their ability to perform activities of daily living (ADL) in the 30 days prior to surgery and immediately before surgery, were also considered. We evaluated the physical status classification by the American Society of Anesthesiologists (ASA) and considered pre-existing comorbidities, including the cardiovascular status, respiratory status, renal status, hematological status, oncological status, preoperative blood transfusion, chronic steroid use, ascites, sepsis, diabetes, open wound, and pregnancy. The laboratory parameters included in the analysis were the white blood cell count, hemoglobin level, hematocrit, platelet count, prothrombin time, and activated partial thromboplastin time, as well as the serum levels of albumin, total bilirubin, aspartate amino transferase, alanine aminotransferase, alkaline phosphatase, urea nitrogen, creatinine, sodium, hemoglobin A1c, and C-reactive protein. The length of surgery, intraoperative blood loss, amount of transfusion, and any accident during the operation were also considered.

Postoperative outcomes evaluated 30 days after surgery were categorized according to the Clavien and Dindo classification [14]. The outcomes included relaparotomy within 30 days after surgery, wound events, anastomotic leak, respiratory events, urinary tract events, central nervous system events, cardiac events, other events, systemic sepsis, sepsis, systemic inflammatory response syndrome, and 24 other complications added by the NCD. For Hx procedures, the indications for surgery and resected subsegments (S1–S8) were included as preoperative variables to create risk models [9].

Outcome measures and statistical analysis

The outcome measures of this study were 30-day mortality and operative mortality. The former was defined as death within 30 days of surgery, regardless of the patient's geographical location, even if the patient had been discharged from hospital. The latter was defined as death within the index hospitalization period, regardless of the length of hospital stay (up to 90 days), as well as any death after discharge, up to 30 days after surgery. Data were randomly

Table 1 Registered cases used to create risk models for 8 surgical procedures [6–13]

	Eso	TG	DG	RHC	LAR	Hx	PD	ADP
Registered cases	5354	20,011	33,917	19,070	16,695	7732	8575	8482
Participating hospitals	713	1623	1737	1689	1620	987	1167	1285
(%)	34.9	79.4	84.9	82.6	79.2	48.3	57.1	62.8
30-day mortality (%)	1.2	0.9	0.5	1.1	0.4	2.0	1.2	9.0
Operative mortality (%)	3.4	2.3	1.2	2.3	0.9	4.0	2.8	14.1
Cancer surgery (%)	98.4	98.5	99.9	92.6	98.5	94.5	91.4	10.8
Emergent case (%)	0.8	2.0	0.9	8.4	1.1	0.8	0.9	92.9

Esophagectomy (Eso), total/distal gastrectomy (TG/DG), right hemicolectomy (RHC), low anterior resection (LAR), hepatectomy performed for >1 segment except for the lateral segment (Hx), pancreaticoduodenectomy (PD), and operation for acute diffuse peritonitis (ADP)

assigned into two subsets that were split 80/20: the first, for model development, and the second, for validation. The two sets of logistic models (30-day mortality and operative mortality) were constructed for dataset development using step-wise selection of the predictors with a probability (p) value for inclusion of 0.05. A "goodness-of-fit" test was performed to assess how well the model could discriminate between patient survival and death. The receiver operating characteristic (ROC) curves for the 30-day and operative mortalities were created for the validation dataset. An ROC curve is a plot of a test's true-positive rate (sensitivity) versus its false-positive rate (1—specificity). Model calibration, being the degree to which the observed outcomes matched the predicted outcomes from the model across a group of patients, was examined by comparing the observed and predicted averages with each of 10 equally sized subgroups, arranged in the order of increasing patient risk.

Case number and participating hospitals for each procedure and mortality rates

The NCD is a nationwide project in cooperation with Japan's board certification system in surgery, for which more than 1,200,000 surgical cases from over 3500 hospitals were collected in 2011. The number of participating hospitals in the gastroenterological section was 2045 at the time of the analysis (July, 2012). Among these cases, approximately 120,000 were used to create the risk models. Table 1 lists the number of cases for each procedure and the number of hospitals performing the respective procedure with its ratio to the total number of hospitals (%). Most procedures, except for ADP, were performed for cancer. Emergency surgery was most common for ADP (93 %). The 30-day mortality and operative mortality rates for the eight procedures were as follows: Eso, 1.2/3.4; TG, 0.9/2.3; DG, 0.5/1.2; RHC, 1.1/2.3; LAR, 0.4/0.9; HX, 2.0/4.0; PD, 1.2/2.8; and ADP, 9.0/14.1 %, respectively (Table 1). The operative mortality for each procedure, apart from ADP, was more than twice that of the 30-day mortality.

Risk models in the eight procedures

The 30-day mortality and operative mortality risk models for the eight procedures were created, and the C-index for those in the validation data sets was as follows: Eso, 0.767/0.742; TG, 0.811/0.824; DG, 0.785/0.798; RHC, 0.836/0.854; LAR, 0.75/0.766; HX, 0.714/0.761; PD, 0.675/0.725; and ADP, 0.851/0.852, respectively (Tables 2, 3). The final logistic models for the 30-day mortality with odds ratios for the eight procedures are listed in Table 2. Age; sex; emergency surgery; ADL; ASA class; BMI; cardiovascular, pulmonary, and renal comorbidities; and other patient conditions such as disseminated cancer, ascites, preoperative transfusion, bleeding disorder, diabetes, weight loss, sepsis, and chronic steroid use, including 121 variables, were found to be risk factors for certain procedures. Age, ADL ASA, BMI, disseminated cancer, bleeding disorder, and weight loss appeared to be common risk factors in most of the procedures. Table 3 lists the final logistic models for the operative mortality with odds ratios for the eight procedures, including 159 variables. New and additional 38 variables were captured for these models.

Feedback implementation (risk calculator)

A risk-adjusted analysis based on nationwide data allows personnel to establish and provide feedback on the risks that patients face before undergoing a procedure. On the basis of these objective data, healthcare professionals can then determine the treatment indicators and obtain informed consent. The risk calculator for all eight procedures will be available soon, on the websites of the hospitals that are a part of NCD, although the calculators for TG, PD, Hx, Eso, RHC, and LAR are currently available (February, 2015). The real-time feedback system gives the predicted mortality of patients simultaneously with data input. Standardized information on patient risk and predicted mortality can be reformulated as case reports and shared at conferences.

Table 2 Risk models for 30-day mortality after 8 gastrointestinal procedures (refs 6–13)

Variables	Eso	TG	DG	RHC	LAR	Hx	PD	ADP
Age category	1.5	1.2	1.2		1.3	1.4	1.3	1.2
Male sex						1.6	2.0	
Ambulance transport								1.4
Emergent surgery				1.9		3.8	4.3	
ADL within 30 days before surgery								
Any assistance	4.2					2.1		
Total			3.0					
ADL immediately before surgery								
Any assistance		2.1		2.8				
Total								1.4
ASA								
Class 3				2.3				2.7
Class 4								4.3
Class 5								8.7
Class 3, 4, 5			2.0			2.0	2.2	
Class 4, 5		9.4		4.0				
BMI								
>25 kg/m^2							2.4	
>30 kg/m^2					7.0			
Congestive heart failure				2.3				
Previous cardiac surgery		2.3						
Myocardial infarction			3.1					
Previous PCI								2.0
Previous PVD surgery					6.2			2.5
Cerebrovascular disease			2.1					
COPD							2.4	
Preoperative pneumonia			2.8					
Respiratory distress								1.6
Acute renal failure				3.2				
Preoperative dialysis		3.9						
Cancer with multiple metastases				2.2				
Disseminated cancer		2.6			4.9			2.2
Preoperative transfusion		1.9			5.4			1.6
Bleeding disorder without treatment			3.2		5.2			1.6
Bleeding disorder							4.4	
Diabetes		2.2						
Smoking within 1 year	2.6							
Ascites		2.0				2.1		
Without control			3.0					
Chronic steroid use								1.7
Weight loss	2.4		2.3					
Sepsis				2.0				
Habitual alcohol consumption			1.6					
WBC								
>12,000/μl	3.7		3.7					
>9000/μl				1.5				
<4000/μl	2.8							1.4

Table 2 continued

Variables	Eso	TG	DG	RHC	LAR	Hx	PD	ADP
Hemoglobin								
M < 13.5 g/dl, F < 12.5 g/dl		1.7	1.8					
<10.0 g/dl								1.3
Platelet								
>400,000/μl	2.5							
<150,000/μl								1.5
<120,000/μl				1.9	5.0	1.7		
<80,000/μl		3.1						1.5
<50,000/μl				5.6				
Albumin								
<4.0 g/dl				2.0	3.4			
<3.5 g/dl		1.7	1.5			2.0		
<2.0 g/dl								1.7
Total bilirubin								
>3.0 mg/dl				3.1				1.7
>2.0 mg/dl		2.9						
AST								
>35 U/l		2.3		3.1		2.3		1.4
ALP								
>600 U/l		2.5						1.7
>340 U/l		1.7	2.2					
BUN								
>25 mg/dl		1.9			2.5			1.4
>20 mg/dl								1.8
<8.0 mg/dl							2.3	
Creatinine								
>2.0 mg/dl						3.9		
>1.2 mg/dl			1.8					
Serum Na								
>145 mEq/l								1.7
<138 mEq/l				2.1	3.6			
<135 mEq/l	3.6		2.5					
<130 mEq/l								1.7
CRP								
<10.0 mg/dl								1.5
APTT								
>40 s							3.2	
PT-INR								
>1.25		2.2	2.0					
>1.1	2.0			1.5		1.7		
Non-tumor bearing								0.6
Surgical procedures						#1		
Indication for surgery						#2		

#1 Hepatectomy with S8 (2.2), hepatectomy with revascularization (3.8)

#2 Hilar bile duct carcinoma (2.5), gallbladder cancer (4.1)

ADL, Activities of daily living, PT-INR Prothrombin time-international normalized ratio, *WBC* white blood cells, *ASA* American society of anesthesiologists, *ADL* activities of daily living, *PCI* percutaneous coronary intervention, *COPD* chronic obstructive pulmonary disease, *AST* aspartate amino transferase, *ALP* alkaline phosphatase, *APTT* activated partial thromboplastin time

Table 3 Risk models for operative mortality after 8 gastrointestinal procedures [6–13]

Variables	Eso	TG	DG	RHC	LAR	Hx	PD	ADP
Age category	1.4	1.3	1.3	1.1	1.4	1.4	1.3	1.3
Male sex	2.3				1.9	1.5		
Emergent surgery		1.7	1.9	1.9		2.8		
ADL within 30 days before surgery								
Any assistance	4.7					2.8	2.5	
Total								1.6
ADL immediately before surgery								
Any assistance		2.0		2.5	2.5			1.4
Total			3.0		2.9			
ASA								
Class 3		1.8		1.6				2.3
Class 4								4.7
Class 5								6.5
Class 3, 4, 5			1.9			2.0	2.1	
Class 4, 5		5.2		2.9				
BMI								
>25 kg/m^2							1.9	
>30 kg/m^2					4.6			
Congestive heart failure				2.2				
Angina							2.6	
Previous PVD surgery				3.1	5.8			
Cerebrovascular disease			1.8					
Cerebrovascular accident		1.9						
Respiratory distress								
Any		1.7	2.4		2.9		2.4	
COPD	2.1					2.0		
Preoperative pneumonia						3.8		1.4
Preoperative dialysis		2.6		2.1				
Cancer metastasis/relapse	4.5			1.6				
Disseminated cancer		3.5	2.9	3.1	2.8			2.1
Preoperative transfusion					2.6			1.8
Bleeding disorder without therapy								1.6
Brinkman index							1.6	
Ascites								
Any		1.8		1.6	4.0	1.9		
Without control			2.8					
Chronic steroid use			2.8	2.0				1.9
Weight loss	2.0	1.6	2.2	1.6			2.1	1.4
Sepsis				1.7				
WBC								
>11,000/μl		2.0	2.5				3.1	
>9000/μl				1.6				
<4500/μl	1.8							1.5
<3500/μl		1.6						
Hemoglobin								
M < 13.5 g/dl, F < 12.5 g/dl					2.6			1.3
<10 g/dl						1.8		
Hematocrit								
M > 48 %, F > 42 %					3.6			

Table 3 continued

Variables	Eso	TG	DG	RHC	LAR	Hx	PD	ADP
M < 37 %, F < 32 %			1.4	1.4				
<30 %		1.3						1.2
Platelet								
<120,000/μl	2.0		2.0	1.7	3.4	1.6	2.1	1.4
<80,000/μl				2.6		2.1		
Albumin								
<3.8 g/dl			1.7					
<3.5 g/dl	2.2	1.4				1.6		
<3.0 g/dl		1.4		1.5		1.7		1.4
<2.5 g/dl					2.7			
<2.0 g/dl								1.5
Total bilirubin								
>3.0 mg/dl								2.0
>2.0 mg/dl		2.8	2.6					
>1.0 mg/dl				1.6				
AST								
>40 U/l			1.5	2.7	1.9	1.7		
>35 U/l		1.7						1.4
ALP								
>600 U/l		3.1						1.6
>340 U/l			1.6					
BUN								
>60 mg/dl				2.4				
>25 mg/dl								1.3
>20 mg/dl								1.8
<8 mg/dl	2.6			1.6				
Creatinine								
>2.0 mg/dl								1.5
>1.2 mg/dl			1.8					
Serum Na								
>145 mEq/l				1.9				
<138 mEq/l	2.1	1.4		1.9	2.5			
<135 mEq/l			2.3					
<130 mEq/l								1.8
CRP								
<10.0 mg/dl								1.5
APTT								
>40 s			1.6				2.0	
PT-INR								
>1.25	3.0	1.9						
>1.1			1.5	1.4		1.4	1.5	
Non-tumor bearing								0.5
Surgical procedure		#1				#2		
indication for surgery						#3		

#1 Pancreatico splenectomy (2.2)

#2 Hepatectomy with S1 (1.6), S7 (1.6), S8 (2.0), left tri-segmentectomy with S1 resection (3.9), hepatectomy with revascularization (3.0)

#3 Intrahepatic cholangiocarcinoma (1.8), hilar bile duct carcinoma (2.0), gallbladder cancer (3.2)

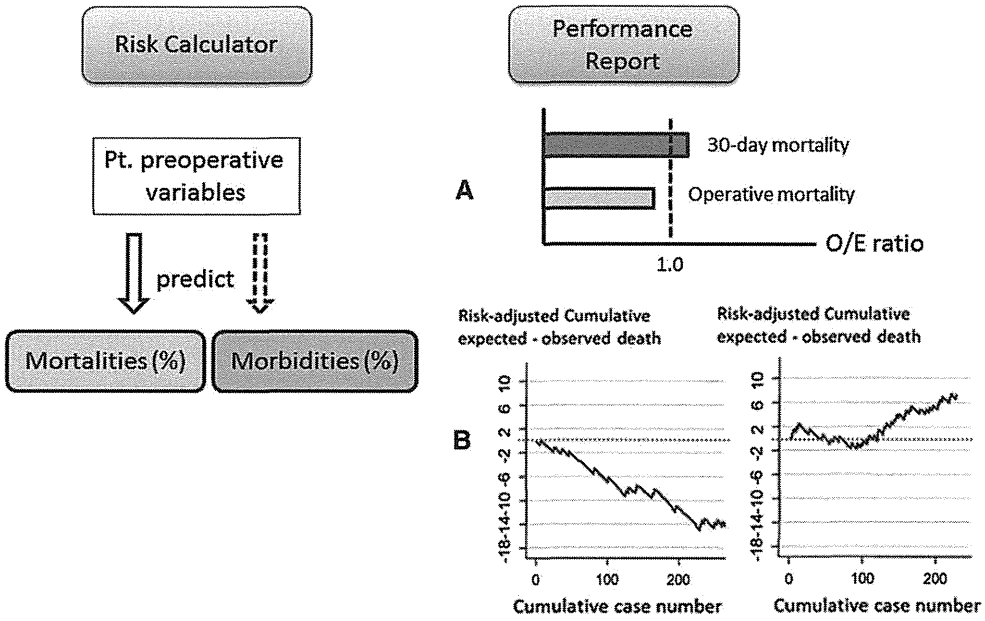

Fig. 1 The National Cancer Database feedback system includes a risk calculator for the mortality and morbidity of preoperative patients (*left schema*) and performance reports of each participating hospital (*right schema*). The latter includes each facility's severity-adjusted clinical performance (*benchmark*) in comparison with the national data (**a**) and the risk-adjusted cumulative expected–observed death (**b**). Better (*right*) or worse (*left*) outcomes can be detected by the monitoring report

The NCD will soon be able to provide data on each facility's severity-adjusted clinical performance (benchmark), which can be compared with national data (Fig. 1a). Cumulative observed–expected mortality can be traced periodically after each operation and used to detect special cause variations showing better (right) and worse (left) outcomes (Fig. 1b).

Future evolution of NCD

A complete data acquisition system link to board certification

More than 4,000,000 cases were retrieved from the NCD during the 3 years before April 2013. The number of esophagectomy and pneumonectomy cases registered in the NCD accounted for approximately 95 % of all cases registered in the Regional Bureau of Health and Welfare. Thus, most cases in Japan appear to be captured by the NCD system. This NCD project started with support from Health and Labor Sciences Research Grants by the Ministry of Health Labour and Welfare (Principal Investigators; MG, T.I.) and considerable funding from the JSGS and JSS. Participating institutions can now use the database system at no cost; however, it is mandatory for the institutions to participate in the benchmarking project when applying for the board certification system. Currently, the board certification system is operating adequately on the web for surgical society members and allows members to obtain information on their cases being used to assess a member's qualifications for certification during a certain period. Any applicant who has a sufficient number of cases for application no longer needs to write case reports. All participating healthcare professionals use information acquired from the NCD. Moreover, the board certification system itself can be revalidated using the surgical improvement program of the NCD.

Share benefits and costs of the NCD with relevant stakeholders

A previous study by Hall et al. [5] showed that participation in the benchmark reporting system of the ACS-NSQIP improved surgical outcomes across all participating hospitals in the private sector. Improvement is reflected for both poor- and well-performing facilities. They speculated in the model using 183 participating hospitals that each institution may have avoided 200–500 complications and 12–36 deaths. Participation in the ACS-NSQIP benefits patients, surgeons, and hospitals and costs 10,000–29,000 (US$) depending on the ACS-NSQIP options [15.]

In the gastroenterological section, risk models of mortality for the eight procedures were created to enable feedback. Simultaneously, risk models of morbidities for the eight procedures are being created to enable feedback for the next year. Currently, the database system is built up to enable efficient provision of benchmark reports to each institute. The benefits and costs can now be shared with the relevant stakeholders. A participation fee depending on the number of cases for retrieval is expected to be charged by the NCD to each hospital. Research grants from various sources are also expected to support clinical investigations using the NCD data.

Eliminating burden on physicians and maintaining data accuracy

To avoid burdening physicians, the NCD allows data entry by other medical staff members. The NCD data entry privileges allow people other than physicians to enter the data. An appropriate educational system for data managers would be mandatory to maintain the accuracy of data and reduce the burden on physicians. This could be achieved by holding an annual data manager educational meeting and eventually introducing an e-learning system. The JSGS is planning to create an audit committee separately from the NCD, with the goal of achieving accurate data inputs and of educating data managers.

Quality improvement of surgical care for cancer patients

The NCD generalizes site-specific cancer registries by taking advantage of their excellent organizing ability. Some site-specific cancer registries have already been combined with the NCD [16]. Cooperation between the NCD and site-specific cancer registries can establish a valuable platform upon which a cancer care plan can be developed in Japan. Furthermore, information on the prognosis of cancer patients gathered using population- and hospital-based cancer registries can enable efficient data accumulation into the NCD.

Currently, quality assessment of hospitals is being carried out using the Diagnosis Procedure Combination (DPC) data from the participating hospitals [17, 18]. The DPC data include variables for preoperative morbidities, cancer variables, and postoperative complications, but they are based mainly on administrative claim data. A low participation rate by very small hospitals in the DPC system covers 50% of institutions conducting surgical services [17] and hampers complete enumeration. The NCD is a quality assessment and improvement program in which clinical data are used with a high collection rate (95 %). Site-specific cancer registries in the NCD would not only be more accurate and suitable for perioperative assessment, but also for long-term outcomes of cancer patients.

Further improvements through transparency

Public reporting and transparency are being demanded by multiple stakeholders [19, 20]. Although it has been shown that performance data released to the public promote quality improvement activity at the hospital level [21, 22], opponents counter that public reporting induces gaming and other unintended consequences such as "cherry picking" (hospitals selecting lower-risk patients to avoid poorer outcomes) or losing patients to better-performing hospitals [23]. With the consent of participating surgical societies, the NCD stated that the performance of each institute would be fed back only to respective institutes but not to the general public. This practice is similar to that of the ACS-NSQIP, from which a report is prepared for administrators and surgical services staff to compare their risk-adjusted surgical outcomes with those of participating sites that are blinded to data other than their own.

In 2012, the ACS-NSQIP partnered with the Centers for Medicare and Medicaid Services (CMS) to promote public reporting and transparency of surgical outcomes [24]. Although there were few measurable differences between CMS-NSQIP-participating and CMS-NSQIP-nonparticipating hospitals, it was found that of all possible hospital structural characteristics, only the teaching hospital status predicted participation in the CMS-NSQIP public reporting initiative. It may be a challenge for participating hospitals to show their performance to the general public. There is an interesting study by Sherman et al. [25, who investigated surgeons' perceptions of public reporting of hospital and individual surgeon quality. They stated that surgeons recommended patient education, simplified data presentation, and continued risk-adjustment refinement, and conducted an internal review before public reporting to make public reporting more acceptable for them. Linkage between hospital information systems and the NCD registry system may improve data accuracy and save costs. Presentation of care quality is increasingly regarded as imperative to support patients' choice and efficiency of care provision. We want medical professionals to realize that good to great performance can be achieved only through transparency for providers and patients.

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Cancer Medicine

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ORIGINAL RESEARCH

Body mass index and survival after diagnosis of invasive breast cancer: a study based on the Japanese National Clinical Database—Breast Cancer Registry

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Keywords
Body mass index, breast cancer, menopausal status, subtypes, survival

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Abstract

Few studies have reported the association between body mass index (BMI) and outcome among Asian breast cancer patients. We analyzed data for 20,090 female invasive breast cancer patients who had been followed-up for a median period of 6.7 years entered in the National Clinical Database–Breast Cancer Registry between 2004 and 2006. We used mainly the WHO criteria for BMI (kg/m^2) categories; <18.5 (underweight), ≥18.5–<21.8 (reference), ≥21.8–<25, ≥25–<30 (overweight), and ≥30 (obese). We divided normal weight patients into two subgroups because this category includes many patients compared to others. The timing of BMI measurement was not specified. The Cox proportional hazards model and cubic spline regression were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs). Smoking, alcohol, and physical activity were not controlled. A total of 1418 all-cause, 937 breast cancer–specific deaths, and 2433 recurrences were observed. Obesity was associated with an increased risk of all-cause (HR: 1.46; 95% CI: 1.16–1.83) and breast cancer–specific death (HR: 1.47; 95% CI: 1.11–1.93) for all patients, and with all-cause (HR: 1.47; 95% CI: 1.13–1.92) and breast cancer–specific death (HR: 1.58; 95% CI: 1.13–2.20) for postmenopausal patients. Being underweight was associated with an increased risk of all-cause death for all (HR: 1.41; 95% CI: 1.16–1.71) and for postmenopausal patients (HR: 1.45; 95% CI: 1.15–1.84). With regard to subtype and menopausal status, obesity was associated with an increased risk of breast cancer–specific death for all cases of luminal B tumor (HR: 2.59; 95% CI: 1.51–4.43; $P_{heterogeneity}$ of Luminal B vs. Triple negative = 0.016) and for postmenopausal patients with luminal B tumor (HR: 3.24; 95% CI: 1.71–6.17). Being obese or underweight is associated with a higher risk of death among female breast cancer patients in Japan.

Introduction

Obesity defined in terms of body mass index (BMI) is a possible factor affecting the prognosis of patients with breast cancer. A previous meta-analysis including 43 studies showed that obesity was associated with higher risk of all-cause or breast cancer–specific death among pre- and postmenopausal women [1]. A more recent large-scale meta-analysis of 82 studies conducted by the World Cancer Research Fund and American Institute for Cancer Research (WCRF/AICR) also showed that obese patients had poorer overall and breast cancer survival, for both pre- and postmenopausal patients, and that being underweight was not associated with breast cancer survival, although the latter included only 10 studies [2].

It has been suggested that associations between BMI and outcome in Asians may differ from those in Europe [3]. A large-scale study from Korea including 24,698 breast cancer patients demonstrated significantly lower overall and breast cancer–specific survival and a higher risk of recurrence in patients who were underweight than in those of normal weight, although no conclusion was drawn with regard to any association between overweight/obesity and breast cancer recurrence or death [4]. A recent study from Japan suggested that both higher BMI and lower BMI are associated with an increased risk of mortality among breast cancer patients [5]. However, the associations between being obese or underweight and survival among breast cancer patients have not been adequately assessed in Asian countries; previous meta-analyses of Asian patients included only two [1] and seven [2] studies, respectively.

There is biological evidence that breast cancer is a heterogeneous disease [6, 7]. There is considerable heterogeneity of breast cancer subtypes, each showing a distinct gene-expression profile [6, 8]. Biological heterogeneity defined by combined estrogen/progesterone receptor (ER/PR) and human epidermal growth factor receptor 2 (HER2) status may imply important differences in tumor etiology and prognosis [9]. Thus, assessment of associations between BMI and breast cancer prognosis according to tumor subtypes defined by ER/PR/HER2 may shed further light on this relationship. In fact, several studies have already investigated the effects of tumor subtype defined by ER/PR status [10–12]. A recent meta-analysis of 21 studies, including the ER/PR status of breast cancer and menopausal status, showed that obesity impacted negatively on both overall and breast cancer survival irrespective of ER/PR and menopausal status [13]. However, few studies have addressed the association between obesity and survival of breast cancer patients in terms of ER/PR/HER2 status [14, 15].

In this study, we investigated the relationship between BMI and the risk of all-cause death and breast cancer–specific death among breast cancer patients in terms of menopausal status and also tumor subtype using a nationwide database in Japan.

Materials and Methods

Study subjects, database, and clinical information

The Japanese Breast Cancer Society (JBCS) has maintained the Breast Cancer Registry (BCR) supported by the Public Health Research Foundation (Tokyo). Affiliated institutes have voluntarily provided the BCR with data on newly diagnosed primary breast cancer cases through a web-based system since 2004 [16]. The National Clinical Database (NCD) in Japan, which was launched in 2010, is a nationwide prospective web-based registry linked to the surgical board certification system. Detailed information about the NCD has been published previously [17, 18]. In brief, the NCD systematically collects accurate data in order to develop a standardized database for improvement of quality and evaluation of healthcare quality from the standpoint of structure, process, and outcome [17]. Detailed information on cancers, such as gastrointestinal, liver, pancreas, thyroid, and breast cancer, is also collected [19]. The NCD contains >1.2 million surgical cases collected up to 2011, and approximately 4000 institutions have been participating. The NCD continuously communicates with hospital personnel responsible for data collection through the NCD web-based data management system, and also consistently performs random site visits to validate the submitted data. Between 2004 and 2011, 238,840 cases were transferred from the JBCS to the NCD for creation of the National Clinical Database—Breast Cancer Registry (NCD-BCR). For our present study, we used NCD-BCR data for 53,670 patients who had been newly diagnosed and registered as having breast cancer at 388 institutions between 2004 and 2006 and who were requested to attend for initial follow up at around 8 years after initial diagnosis. An estimate of newly diagnosed female breast cancer cases between 2004 and 2006 is 155,027 [20]. Newly diagnosed breast cancer cases captured in this registry are 34.6%. Finally, 25,898 patients from 170 institutions were followed up.

Information on patients covering age, sex, height and weight, place of residence, detection method, family history of breast cancer, menopausal status, tumor characteristics, TNM classification, and treatment (chemotherapy, endocrine therapy, radiation therapy) was obtained from the NCD-BCR. The TNM classification and histological classification were registered according to the UICC staging [21] and WHO classification systems, [22] respectively. Patients who were male (n = 231) or of unknown sex

(n = 1), or who were at stage 0 (n = 5546) or IV (n = 1355) or unknown stage (n = 1349) were excluded, leaving a total of 45,188 patients. Information on ER/PR/HER2 was also obtained from the NCD-BCR. ER/PR positivity was diagnosed if at least 1% of nuclei in the tumor were immunohistochemically positive for ER or PR. HER2 overexpression was defined as an immunohistochemical score of 3 + and/or a positive FISH result. Cases were categorized into four subtypes on the basis of their status: luminal A (ER+/PR+/HER2−); luminal B (ER+/PR−/HER2− or ER+/HER2 +); HER2− overexpressing (ER−/PR−/HER2 +); and triple negative (ER−/PR−/HER2−) [23].

Ascertainment of exposures and follow up

Body mass index was calculated as weight divided by the square of height (kg/m^2). Patients whose height or body weight was unknown (n = 2582) were excluded, as were those whose age (n = 206) and place of residence (n = 10) were unknown, leaving a total of 42,390 patients. We categorized BMI into a five-level variable with reference to the WHO criteria, [24] using a median value of 21.8 between 18.5 and 25.0: <18.5 (underweight), ≥18.5–<21.8 (reference), ≥21.8–<25.0, ≥25.0–<30.0 (overweight), and ≥30 (obese).

Figure 1 shows a flow diagram of this study. Information on the date of follow up and status (alive, death from breast cancer, death due to causes other than breast cancer, and death due to unknown causes) and the date of recurrence and status (with or without recurrence) were obtained from the NCD-BCR. During the study period, 20,090 (47.4%) patients were followed up.

Statistical analysis

The endpoint of our analysis was all-cause death, breast cancer–specific death, and recurrence. Recurrence included local (conserved breast, chest wall, axillary lymph nodes, and regional lymph nodes) and distant (lung, liver, bone, brain, distant lymph nodes, pleura, and others) metastasis. Survival time was calculated for each patient from the date of first treatment to the date of death, recurrence, or the end of follow up. We used date of first treatment instead of date of diagnosis because the NCD-BCR does not have date of diagnosis.

The Cox proportional hazards model was used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for all-cause death, breast cancer–specific death, and recurrence in relation to BMI [25]. Dose–response relationships were tested by treating each exposure category as a continuous variable and were employed in the Cox model for BMI ≥18.5 because we expected the overall relationship of BMI to each endpoint to be U shaped rather than linear (i.e., we expected patients with BMI <18.5 have higher mortality than the reference category). To evaluate a potential non-linear relationship between BMI and each endpoint, we applied cubic splines with three knots in settled percentiles (10%, 50%, and 90%) of the distribution to model the possible association [26].

We considered the following variables to be potential confounders: age, place of residence (eastern Japan, western Japan), detection method (self-detection, screening with symptoms, screening without symptoms, others), family history of breast cancer (no, yes), tumor stage [Stage I,

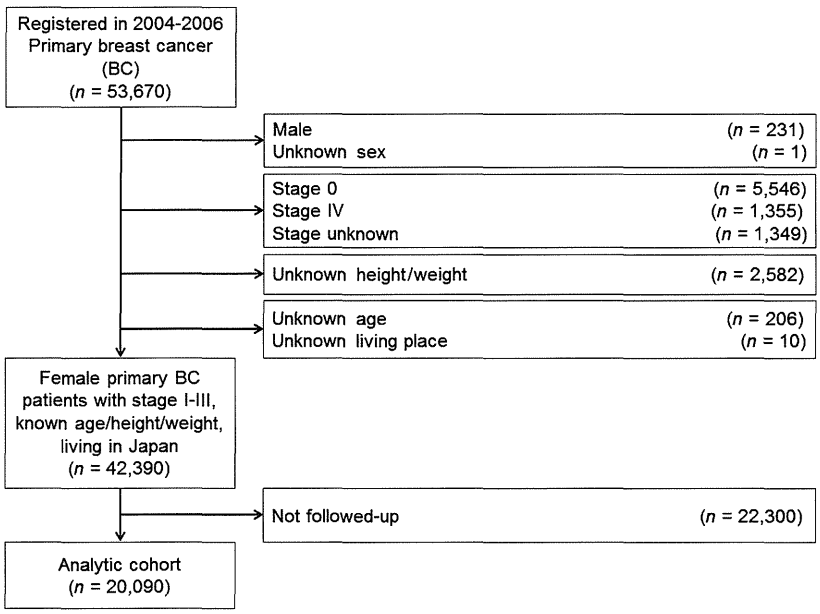

Figure 1. Study flow.

Table 1. Patient characteristics.

			BMI									
	Total (*N* = 20,090)		<18.5 (*N* = 1561)		≥18.5–<21.8 (*N* = 6833)		≥21.8–<25 (*N* = 6784)		≥25–<30 (*N* = 4015)		≥30 (*N* = 897)	
	N	%	*N*	%	*N*	%	*N*	%	*N*	%	*N*	%
All-cause death	1418	7.1	138	8.8	414	6.1	476	7.0	298	7.4	92	10.3
Breast cancer–specific death	937	4.7	73	4.7	287	4.2	323	4.8	191	4.8	63	7.0
Recurrence	2433	12.1	193	12.4	796	11.7	839	11.7	478	11.9	127	14.2
Age (year)												
Mean (SD)	57.3	12.8	54.8	14.7	54.0	12.9	58.6	12.1	60.9	11.9	59.7	11.9
Median	57.0		53.0		53.0		58.0		61.0		60.0	
Follow up												
Median	6.7		6.5		6.7		6.7		6.7		6.6	
Person years	119873.4		8875.8		40967.5		40681.3		24062.4		5286.3	
Living place												
Eastern Japan	9598	47.8	737	47.2	3247	47.5	3260	48.1	1917	47.8	437	48.7
Western Japan	10,492	52.2	824	52.8	3586	52.5	3524	52.0	2098	52.3	460	51.3
Detection method												
Self–detection	14,736	73.4	1219	78.1	4988	73.0	4885	72.0	2948	73.4	696	77.6
Screening with symptom	1203	6.0	81	5.2	441	6.5	402	5.9	235	5.9	44	4.9
Screening without symptom	3131	15.6	175	11.2	1092	16.0	1130	16.7	625	15.6	109	12.2
Others	1020	5.1	86	5.5	312	4.6	367	5.4	207	5.2	48	5.4
Family history of breast cancer												
No	17,078	85.0	1337	85.7	5827	85.3	5762	84.9	3392	84.5	760	84.7
Yes	1761	8.8	132	8.5	589	8.6	604	8.9	364	9.1	72	8.0
Missing	1251	6.2	92	5.9	417	6.1	418	6.2	259	6.5	65	7.3
Tumor stage												
Stage I	8304	41.3	725	46.4	3075	45.0	2765	40.8	1473	36.7	266	29.7
Stage II (IIA/IIB)	9841	49.0	662	42.4	3186	46.6	3376	49.8	2102	52.4	515	57.4
Stage III (IIIA/IIIB/IIIC)	1945	9.7	174	11.2	572	8.4	643	9.5	440	11.0	116	12.9
Treatments												
Chemotherapy												
No	10,638	53.0	889	57.0	3567	52.2	3557	52.4	2154	53.7	471	52.5
Yes	9452	47.1	672	43.1	3266	47.8	3227	47.6	1861	46.4	426	47.5
Endocrine therapy												
No	6524	32.5	539	34.5	2339	34.2	2194	32.3	1220	30.4	232	25.9
Yes	13,566	67.5	1022	65.5	4494	65.8	4590	67.7	2795	69.6	665	74.1
Radiation therapy												
No	10,543	52.5	848	54.3	3408	49.9	3577	52.7	2236	55.7	474	52.8
Yes	9409	46.8	700	44.8	3381	49.5	3161	46.6	1751	43.6	416	46.4
Unknown	138	0.7	13	0.8	44	0.6	46	0.7	28	0.7	7	0.8
Tumor subtypes												
Luminal A	9850	49.0	732	46.9	3252	47.6	3272	48.2	2084	51.9	510	56.9
Luminal B	3988	19.9	327	21.0	1378	20.2	1383	20.4	754	18.8	146	16.3
HER2	1485	7.4	122	7.8	542	7.9	523	7.7	258	6.4	40	4.5
Triple negative	2993	14.9	227	14.5	1064	15.6	1028	15.2	556	13.9	118	13.2
Others	1774	8.8	153	9.8	597	8.7	578	8.5	363	9.0	83	9.3
Menopausal status												
Premenopausal	6785	33.8	696	44.6	3065	44.9	1923	28.4	879	21.9	222	24.8
Postmenopausal	12576	62.6	814	52.2	3524	51.6	4611	68.0	2987	74.4	640	71.4
Unknown (including surgery)	729	3.6	51	3.3	244	3.6	250	3.7	149	3.7	35	3.9
Registered year												
2004	6368	31.7	468	30.0	2157	31.6	2195	32.4	1302	32.4	246	27.4
2005	7199	35.8	561	35.9	2432	35.6	2428	35.8	1434	35.7	344	38.4
2006	6523	32.5	532	34.1	2244	32.8	2161	31.9	1279	31.9	307	34.2

BMI, body mass index.

Stage II (IIA/IIB), Stage III (IIIA/IIIB/IIIC)], chemotherapy (no, yes), endocrine therapy (no, yes), radiation therapy (no, yes, unknown), tumor subtype (luminal A, luminal B, HER2, triple negative, others), menopausal status (premenopausal, postmenopausal, unknown), and registration year (2004, 2005, 2006).

Separate analyses were conducted after dividing the patients according to menopausal status and tumor subtype, along with analysis of the patients overall. Menopause was defined as the cessation of menstrual periods for more than 1 year. Menopause resulting from surgery was defined as unknown menopausal status. To evaluate heterogeneity of the associations between BMI and each endpoint across tumor subtypes (Luminal B vs. Luminal A/ HER2− overexpressing/triple negative), interaction terms (BMI * tumor subtypes) were tested.

Results were regarded as significant if the two-sided P values were <0.05. All statistical analyses were performed using the SAS 9.4 (SAS Institute, Cary, NC).

Results

The patient characteristics are shown in Table 1. During a median follow-up period of 6.7 years, 1418 all-cause deaths, 937 breast cancer–specific deaths, and 2433 recurrences were observed. Obese patients were more likely to have an advanced stage of breast cancer, a luminal A tumor, or to have undergone endocrine therapy. Underweight patients were more likely to have self-detected tumors, and less likely to have undergone chemotherapy.

Table 2 shows the association of BMI with each endpoint. Compared to patients with BMI ≥18.5–<21.8, those with BMI ≥30.0 were shown to have a higher risk of all-cause death (HR: 1.46; 95% CI: 1.16–1.83; $P = 0.0012$) and breast cancer–specific death (HR: 1.47; 95% CI: 1.11–1.93; $P = 0.0065$). A dose–response relationship was observed between BMI and all-cause death ($P_{trend} = 0.026$). Stratification by menopausal status revealed that postmenopausal obese patients had a higher risk of all-cause death (HR: 1.47; 95% CI: 1.13–1.92; $P = 0.0045$) and breast cancer–specific death (HR: 1.58; 95% CI: 1.13–2.20; $P = 0.0072$). For premenopausal women, our results showed that obesity was associated with non-significant higher risks of all-cause death (HR: 1.46; 95% CI: 0.91–2.35) and breast cancer–specific death (HR: 1.34; 95% CI: 0.79–2.27). Underweight patients had a higher risk of all-cause death among patients as a whole (HR: 1.41; 95%

Table 2. HR (95% CI) of each endpoint with BMI overall and by menopausal status.

		All-cause death				Recurrence				Breast cancer–specific death			
BMI	Cases	Events	HR	95% CI	*P*	Events	HR	95% CI	*P*	Events	HR	95% CI	*P*
All													
≥30	897	92	1.46	1.16–1.83	0.0012	127	1.15	0.95–1.39	0.15	63	1.47	1.11–1.93	0.0065
≥25–<30	4015	298	1.04	0.90–1.21	0.58	478	0.97	0.87–1.09	0.61	191	1.03	0.86–1.24	0.75
≥21.8–<25	6784	476	1.02	0.90–1.17	0.74	839	1.02	0.93–1.13	0.68	323	1.03	0.88–1.21	0.72
≥18.5–<21.8	6833	414	Reference[1]			796	Reference[1]			287	Reference[1]		
<18.5	1561	138	1.41	1.16–1.71	0.0005	193	1.09	0.94–1.28	0.26	73	1.16	0.90–1.50	0.27
P_{trend}					0.026				0.6				0.067
Premenopausal													
≥30	222	20	1.46	0.91–2.35	0.12	35	1.21	0.85–1.71	0.29	16	1.34	0.79–2.27	0.28
≥25–<30	879	62	1.10	0.81 –1.49	0.54	121	1.00	0.81 –1.23	0.99	54	1.09	0.78 –1.50	0.63
≥21.8–<25	1923	98	0.90	0.69–1.17	0.44	225	0.91	0.77–1.08	0.26	81	0.86	0.64–1.14	0.29
≥18.5–<21.8	3065	140	Reference[2]			364	Reference[2]			122	Reference[2]		
<18.5	696	32	1.08	0.74–1.59	0.69	72	0.86	0.67–1.11	0.24	23	0.91	0.58–1.43	0.68
P_{trend}					0.21				0.71				0.39
Postmenopausal													
≥30	640	70	1.47	1.13–1.92	0.0045	88	1.15	0.92–1.46	0.23	46	1.58	1.13–2.20	0.0072
≥25–<30	2987	228	1.01	0.84–1.20	0.95	335	0.96	0.83–1.11	0.55	131	1.02	0.80–1.28	0.9
≥21.8–<25	4611	354	1.02	0.87–1.20	0.78	570	1.06	0.93–1.20	0.39	229	1.11	0.91–1.36	0.31
≥18.5–<21.8	3524	264	Reference[2]			414	Reference[2]			156	Reference[2]		
<18.5	814	97	1.45	1.15–1.84	0.0018	113	1.19	0.97–1.47	0.1	45	1.22	0.88–1.71	0.24
P_{trend}					0.11				0.82				0.11

HR, hazard ratio; CI, confidence interval; BMI, body mass index.

[1]Adjusted by age, living place, detection method, family history of breast cancer, tumor stage, radiation therapy, chemotherapy, endocrine therapy, tumor subtypes, menopausal status, and registered year.

[2]Adjusted by age, living place, detection method, family history of breast cancer, tumor stage, radiation therapy, chemotherapy, endocrine therapy, tumor subtypes, and registered year.

Table 3. HR (95% CI) of each endpoint with BMI by tumor subtypes.

			Recurrence				Breast cancer–specific death		
BMI	Cases	Events	HR	95% CI	*P*	Events	HR	95% CI	*P*
Luminal A									
≥30	510	50	1.23	0.90–1.68	0.19	17	1.64	0.93–2.90	0.087
≥25–<30	2084	173	1.07	0.87–1.31	0.53	49	1.27	0.84–1.92	0.26
≥21.8–<25	3272	258	1.11	0.92–1.33	0.27	56	1.05	0.71–1.56	0.81
≥18.5–<21.8	3252	221	1.00 (Reference)			46	1.00 (Reference)		
<18.5	732	63	1.24	0.93–1.64	0.14	15	1.39	0.77–2.49	0.27
P_{trend}					0.25				0.075
Luminal B									
≥30	146	26	1.16	0.77–1.75	0.49	18	2.59	1.51–4.43	0.0006
≥25–<30	754	98	0.87	0.68–1.12	0.27	38	1.14	0.75–1.74	0.54
≥21.8–<25	1383	196	1.01	0.83–1.24	0.9	59	1.07	0.73–1.54	0.74
≥18.5–<21.8	1378	194	1.00 (Reference)			56	1.00 (Reference)		
<18.5	327	41	0.97	0.70–1.37	0.88	15	1.32	0.75–2.35	0.34
P_{trend}					0.68				0.017
HER2									
≥30	40	12	1.24	0.68–2.26	0.49	7	1.53	0.68–3.42	0.3
≥25–<30	258	46	0.74	0.52–1.05	0.094	13	0.43	0.23–0.80	0.0077
≥21.8–<25	523	112	0.93	0.72–1.22	0.61	43	0.73	0.48–1.10	0.13
≥18.5–<21.8	542	114	1.00 (Reference)			50	1.00 (Reference)		
<18.5	122	25	0.95	0.61–1.47	0.8	12	0.99	0.52–1.89	0.98
P_{trend}					0.32				0.097
Triple negative									
≥30	118	29	1.09	0.74–1.62	0.67	18	1.11	0.67–1.84	0.68
≥25–<30	556	114	0.95	0.75–1.20	0.66	72	1.03	0.77–1.39	0.84
≥21.8–<25	1028	230	1.08	0.89–1.31	0.44	145	1.15	0.90–1.48	0.26
≥18.5–<21.8	1064	200	1.00 (Reference)			112	1.00 (Reference)		
<18.5	227	50	1.15	0.84–1.57	0.39	24	0.97	0.62–1.51	0.89
P_{trend}					0.97				0.65
Luminal B versus Luminal A – $P_{heterogeneity}$ of trends					0.25				0.7
Luminal B versus HER2 – $P_{heterogeneity}$ of trends					0.56				0.0062
Luminal B versus Triple negative – $P_{heterogeneity}$ of trends					0.79				0.059
Luminal B versus Luminal A – $P_{heterogeneity}$ of BMI ≥30					0.77				0.25
Luminal B versus HER2 – $P_{heterogeneity}$ of BMI ≥30					0.86				0.29
Luminal B versus Triple negative – $P_{heterogeneity}$ of BMI ≥30					0.82				0.016

Adjusted by age, living place, detection method, family history of breast cancer, tumor stage, radiation therapy, chemotherapy, endocrine therapy, menopausal status, and registered year. HR, hazard ratio; CI, confidence interval; BMI, body mass index.

CI: 1.16–1.71; $P = 0.0005$) and among postmenopausal patients (HR: 1.45; 95% CI: 1.15–1.84; $P = 0.0018$).

Table 3 shows the association of BMI with recurrence and breast cancer–specific death according to tumor subtype. Compared to patients with BMI ≥18.5–<21.8, those with BMI ≥30.0 were shown to have a higher risk of breast cancer–specific death (HR: 2.59; 95% CI: 1.51–4.43; $P = 0.0006$; $P_{heterogeneity}$ of Luminal B vs. Triple negative = 0.016) among patients with luminal B tumor. A dose–response relationship was observed between BMI and breast cancer–specific death ($P_{trend} = 0.017$).

Stratification by menopausal status among patients with luminal B tumor (Table 4) revealed that postmenopausal obese patients had a higher risk of breast cancer–specific death (HR: 3.24; 95% CI: 1.71–6.17; $P = 0.0003$). A dose–response relationship was observed between BMI and breast cancer–specific death ($P_{trend} = 0.022$).

Figure 2 shows HR and the corresponding 95% CI of multivariate-restricted cubic splines between BMI and each endpoint. A dose–response relationship was observed between BMI and all-cause death, higher BMI and breast cancer–specific death (Fig. 2A and B) overall. Among postmenopausal patients a dose–response relationship was observed between BMI and all-cause death, higher BMI and breast cancer–specific death (Fig. 2C and D). Among patients with luminal B tumor, a dose–response relationship was observed between higher BMI and breast cancer–specific death overall (Fig. 2E) and postmenopausal patients (Fig. 1F).

Table 4. HR (95% CI) of each endpoint with BMI by menopausal status among luminal B tumor.

			Recurrence				Breast cancer–specific death		
BMI	Cases	Events	HR	95% CI	*P*	Events	HR	95% CI	*P*
Premenopausal									
≥30	30	8	1.41	0.67–3.01	0.37	4	1.95	0.63–6.10	0.25
≥25–<30	114	17	0.97	0.57–1.66	0.91	7	1.07	0.45–2.55	0.87
≥21.8–<25	283	42	0.93	0.63–1.37	0.73	12	0.90	0.44–1.84	0.77
≥18.5–<21.8	481	73	Reference			23	Reference		
<18.5	100	12	0.83	0.45–1.54	0.56	3	0.74	0.22–2.49	0.62
P_{trend}					0.67				0.47
Postmenopausal									
≥30	109	18	1.09	0.66–1.80	0.72	14	3.24	1.71–6.17	0.0003
≥25–<30	613	76	0.81	0.61–1.09	0.16	29	1.19	0.71–1.99	0.5
≥21.8–<25	1054	147	1.02	0.80–1.30	0.89	46	1.27	0.80–2.02	0.31
≥18.5–<21.8	847	118	Reference			31	Reference		
<18.5	215	27	0.95	0.63–1.45	0.81	10	1.39	0.68–2.86	0.37
P_{trend}					0.35				0.022

HR, hazard ratio; CI, confidence interval; BMI, body mass index. Adjusted by age, living place, detection method, family history of breast cancer, tumor stage, radiation therapy, chemotherapy, endocrine therapy, and registered year.

Discussion

Our present study demonstrated that being obese or underweight was associated with an increased risk of death overall, especially for postmenopausal patients. In terms of tumor subtype and menopausal status, obesity was associated with an increased risk of death in patients with luminal B tumor and in patients who were postmenopausal. The association between BMI and survival among breast cancer patients has not been adequately addressed in Asian countries [1, 2]. Our study is therefore of importance in that a nationwide database in Japan has been analyzed for the first time in a prospective setting, involving a large number of breast cancer patients stratified according to tumor subtype and menopausal status.

A meta-analysis including 213,075 breast cancer patients with 41,477 deaths (23,182 from breast cancer) reported that the relative risk (RR) of total mortality for obese patients was 1.41 (95% CI: 1.29–1.53) and that of breast cancer mortality was 1.35 (95% CI: 1.24–1.47) in comparison with patients of normal weight [2]. That study also revealed that the RR of total mortality for obese patients was 1.75 (95% CI: 1.26–2.41) among those who were premenopausal and 1.34 (95% CI: 1.18–1.53) for those who were postmenopausal, whereas the RR of breast cancer mortality was 1.50 (95% CI: 1.13–2.00) for premenopausal women and 1.34 (95% CI: 1.21–1.48) for postmenopausal women in comparison with women of normal weight [2]. Our present results are consistent with these, showing that obesity was associated with a higher risk of all-cause death and breast cancer–specific death for the patients overall and for postmenopausal patients. For premenopausal women, our present results demonstrated that obesity was associated with a nonsignificant higher risk of all-cause death and breast cancer–specific death. One possible reason for this relationship may have been the slightly higher proportion of obese patients with advanced-stage breast cancer. Therefore, we attempted to analyze the data for Stage I breast cancer alone. However, this yielded almost the same results (Table 5). We hypothesized a reason for a slightly higher proportion of obese patients with advanced-stage cancer. This might be due to the development of more aggressive tumors rather than screening behavior. The proportion of TNBC, an aggressive type of tumor, in overweight or obese women was lower than others.

Our present study demonstrated that underweight patients had an increased risk of all-cause death, among both the patients overall and those who were postmenopausal. A previous meta-analysis of 10 studies had shown that being underweight had no association with breast cancer survival [2]. Also a large study of Korean breast cancer patients had shown that underweight patients were at a significantly higher risk of all-cause death (HR: 1.48; 95% CI: 1.15–1.90) [4]. Underweight patients might have included undernourished patients, especially among postmenopausal women, as well as properly nourished, naturally lean patients. In patients showing chronic undernutrition, cytokine reactions and subsequent activation of the immune system are compromised [27]. This may have partly contributed to the increased risk of all-cause death among underweight, postmenopausal women. Another reason for the association between being underweight and the higher risk of all-cause death might have been the slightly higher proportion of patients with advanced-stage breast cancer. Therefore, we attempted to analyze the data by omitting

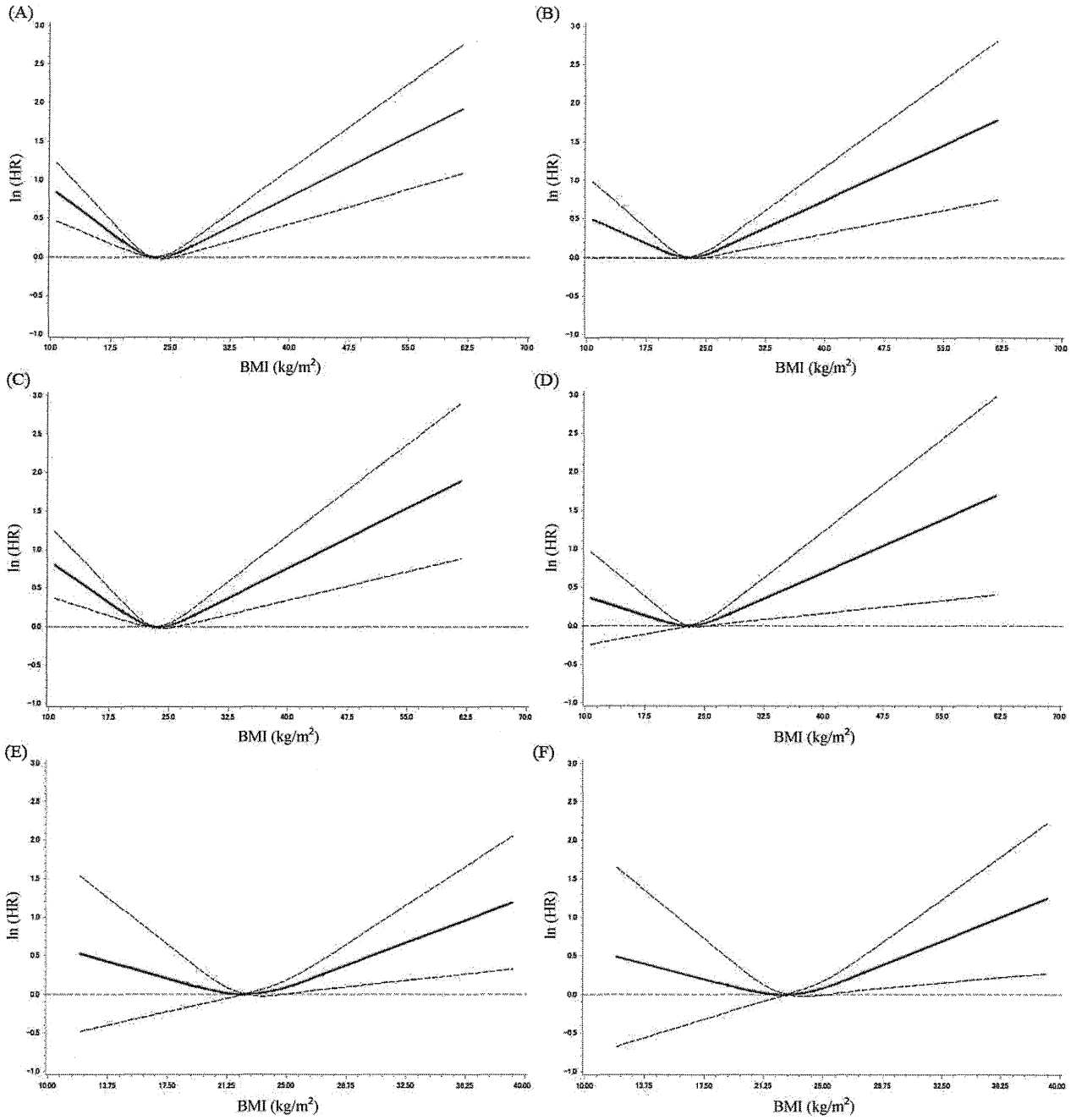

Figure 2. HR (ln of HR) and the corresponding 95% confidence intervals (CIs), using multivariate restricted cubic splines between body mass index (BMI) and each endpoint: (A) all-cause death for all, (B) breast cancer–specific death for all, (C) all-cause death for postmenopausal, (D) breast cancer–specific death for postmenopausal, (E) breast cancer–specific death for all with luminal B tumor, and (F) breast cancer–specific death for postmenopausal with luminal B tumor. The solid line and dash lines indicate HR and 95% CI.

cases of advanced breast cancer. However, this yielded almost the same results (Table 5).

A few studies have reported the association between BMI and survival of breast cancer patients with combined ER/PR/HER2 status [14, 15]. One study found that a higher BMI was associated with shorter disease-free survival in postmenopausal patients, but no independent effect of any specific subtype was observed [14]. The other study showed that patients with ER–/HER2 + tumors showed significantly worse overall survival and that a higher proportion of obese patients had distant metastases [15]. In our present study, an association of obesity with poorer