



Increased prevalence of metabolic syndrome in adult cancer survivors: Asian first report in community setting



Minkyung Kim^a, In-Hoo Kim^a, Min Kyung Lim^a, Yeol Kim^a, Boyoung Park^{b,*}

^a National Cancer Center Graduate School of Cancer Science and Policy, 323 Ilsan-ro, Ilsandong-gu, Goyang, Gyeonggi-do, 10408, Republic of Korea

^b Department of Medicine, Hanyang University College of Medicine, 222 Wangsimni-ro, Seongdong-gu, Seoul, 04763, Republic of Korea

ARTICLE INFO

Keywords:

Cancer survivors
Metabolic syndrome
Prevalence

ABSTRACT

Background: To compare the prevalence of metabolic syndrome (MeS) in cancer survivors returning to the community to that of non-cancer controls.

Methods: We used baseline data from a nationwide cohort study. 5274 cancer survivors and 20,703 and 21,096 gender- and age-matched controls without and with chronic disease was included.

Results: The prevalence of MeS was higher in cancer survivors compared to controls without chronic disease, but was lower than that in controls with chronic disease (25.7%, 18.8%, and 32.0%, respectively). The prevalence was 1.56-fold higher in cancer survivors (95% confidence interval = 1.45–1.69) than in controls without chronic disease. The prevalence of each MeS component was significantly higher in cancer survivors compared to controls without chronic disease. Compared to controls, the prevalence was higher in colorectal, breast, cervical, lung, thyroid, prostate, and bladder cancer survivors (OR range = 1.63–2.24, P-value < 0.05), but not in gastric and liver cancer survivors.

Conclusions: MeS was generally more prevalent among cancer survivors than in controls without chronic disease, but with heterogeneities in cancer type. Because long-term care and comorbidity prevention are emerging issues in cancer survivors, MeS among those returning to normal life is concerning, and tailored management programs should be developed for specific cancer types.

1. Introduction

The increasing incidence of cancer has placed a heavy burden on the management of this disease. Globally, the number of new cases of cancer increased to 14.1 million in 2012 [1]. Along with the increase in the number of incidences, the population of cancer survivors also increases. As of 2014, there were 14.5 million cancer survivors, a number that is expected to increase to 19 million by 2024 [2].

Cancer survivors are prone to increased incidence of comorbidities compared with the general population without a history of cancer [3]. Furthermore, the late effects of cancer treatment may lead to adverse outcomes. Among these outcomes, cardiovascular disease has been reported as one of the most prevalent comorbidities [3], contributing to the largest number of deaths among cancer survivors [4]. Thus, management of cardiovascular disease in cancer survivors has become an important issue. As one of the important predictive factors of cardiovascular disease, metabolic syndrome (MeS) has received increasing attention not only in the general population but also in cancer survivors

[5]. MeS is considered a multiplex cardiovascular risk factor [6] and abnormalities in the clinical markers of MeS may promote the development of cardiovascular events [6]. Therefore, MeS in cancer survivors is an increasingly important issue for its potential cardiovascular disease-related burden, which remains the most common comorbidity in this population. Previous studies have investigated the prevalence of MeS in cancer survivors, but the results were inconsistent and based on limited sample sizes [5,7,8]. Additionally, vulnerability to MeS may differ according to cancer type [5,9–12].

As the number of cancer survivors and their remaining years of life have increased, rehabilitation and health management among those who complete treatment and return to their normal lives have been emerging issues [13]. Management of cancer survivors should include strategies to control short- and long-term treatment complications as well as changes in health conditions after diagnosis or treatment [14,15]. However, most previous studies have considered MeS as a short-term side effect during cancer treatment [16,17]; thus, MeS among cancer survivors living in the general community has been

* Corresponding author.

E-mail addresses: minkyungkim0425@gmail.com (M. Kim), ikim@ncc.re.kr (I.-H. Kim), mickey@ncc.re.kr (M.K. Lim), drheat@ncc.re.kr (Y. Kim), hayejine@hanmail.net (B. Park).

<https://doi.org/10.1016/j.canep.2018.12.006>

Received 23 September 2018; Received in revised form 16 November 2018; Accepted 7 December 2018

Available online 19 December 2018

1877-7821/ © 2018 Elsevier Ltd. All rights reserved.

ignored. As advances in cancer care have been achieved and survival rate after cancer has increased rapidly, cancer is considered a controllable and manageable disease that requires long-term care. In addition, physicians need to consider patients under treatment for cancer as individuals with chronic conditions [18–20]; therefore, the major long-term sequelae in cancer survivors require further investigation, particularly in comparison with patients with or without other chronic diseases. Studies on these topics are limited; thus, these data will help assess whether cancer should be considered a chronic disease.

Thus, this study investigated the prevalence of MeS and each MeS component in cancer survivors living in community compared to the prevalence among control subjects without a history of cancer and with or without chronic disease (CDZ and CNDZ, respectively). In addition, the prevalence of MeS components was compared among various site-specific cancers.

2. Materials and methods

2.1. Study population and definition

As a part of a nationwide cohort study, the Health Examinees (HEXA) study has collected data since 2004, from 173,357 subjects ranging in age from 40 to 79 years, who have provided written informed consent. Conducted at 38 health examination centers in Korea, the study collected data at baseline, using face-to-face interviews to complete structured questionnaires. Information on socio-demographic factors, medical history, family history, smoking and alcohol drinking, physical activity, socio-psychological factors, and reproductive factors was collected. Dietary intake was assessed using a validated semi-quantitative food frequency questionnaire by the Food Composition Table of Korea [21]. The results of physical and clinical laboratory examinations were also obtained.

A total of 5274 cancer survivors self-declared that they had been diagnosed with cancer by a physician. Two control groups—CDZ and CNDZ—were selected based on self-reported medical history. The chronic diseases included hypertension, diabetes, dyslipidemia, stroke, angina or myocardial infarction, gastrointestinal disease, intestinal polyps, fatty liver, chronic liver disease or liver cirrhosis, gallstone/cholecystitis, respiratory disease, thyroid disease, arthritis, osteoporosis, gout, glaucoma or cataracts, and depression, which were associated with MeS in previous studies [22–38]. The controls were randomly matched with cancer survivors in 1:4 ratios by frequency matching according to 5-year age groups and sex. After matching, the study population included 5274 cancer survivors, 20,703 CNDZ, and 21,096 CDZ (Fig. 1). The Institutional Review Board of the National Cancer Center approved this study protocol, which complied with the principles of the Declaration of Helsinki (IRB No: NCC2014-0098).

MeS was diagnosed according to the results of physical and clinical laboratory examinations according to the revised version of the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III). The definition of MeS requires three or more of the following components: 1) abdominal obesity (waist circumference > 90 cm in men or 80 cm in women, the recommended standard for Asian Americans); 2) high triglyceride level (≥ 150 mg/dL or on drug for treatment of hypertriglyceridemia); 3) low level of high-density lipoprotein (HDL) (< 40 mg/dL in men and < 50 mg/dL in women); 4) high blood pressure ($\geq 130/85$ mmHg or on drugs for treatment of hypertension); 5) high fasting plasma glucose level (≥ 100 mg/dL or on drugs for treatment of hyperglycemia) [39].

2.2. Statistical analysis

The distribution of characteristics and MeS between cancer survivors and two matched control groups was compared using analysis of variance (ANOVA) and chi-square tests for continuous and categorical variables, respectively. After ANOVA, posthoc (Duncan) comparisons of

each MeS component were performed.

In order to investigate the MeS prevalence in cancer survivors compared with those in CNDZ and CDZ separately, multivariate conditional logistic regression was performed by adjusting for the following variables: marital status (married/cohabitation and divorced/widowed/unmarried), education level (less than and equal to high school/more than college), household income (< 2000\$/ \geq 2000\$), employment status (currently unemployed/currently employed), self-rated health status (healthy/normal-unhealthy), family history of cancer (yes/no), oral contraceptive use (yes/no), and menopausal status (yes/no). The behavioral risk factors of MeS considered in this study included current smoking status (yes/no), current drinking status (yes/no), exercising status (< 150 min/week/ \geq 150 min/week according to the American Cancer Society's recommendations [40]), body mass index (BMI, < 23 kg/m²/ \geq 23 kg/m² according to the American Diabetes Association's recommendation for Asian Americans [41]), and carbohydrate intake (low/normal/high, as tertiles), which have been associated with MeS in previous studies [7–12,42], using values from the CNDZ as the reference levels. To investigate whether the increment of odds ratios (ORs) for MeS differed significantly between cancer survivors and CDZ, the ORs of both were compared using a heterogeneity test. To identify increased prevalence of MeS in different cancer types, the adjusted ORs for the above covariates were estimated for each type of cancer compared with CNDZ.

P-values < 0.05 were considered to be significant in all analyses. Statistical analyses were performed using SAS 9.3 (SAS Institute, Cary, NC, USA) and STATA version 12 (STATA Corp., Texas, USA) to evaluate the p-heterogeneity.

3. Results

The baseline characteristics of cancer survivors, CDZ, and CNDZ are shown in Table 1. The distribution of marital status, education, household income, employment status, self-rated health status, family history of cancer, current smoking status, current drinking status, exercise, oral contraceptive use, and menopausal status (only for women), which were not included as matching variables, differed significantly between the three groups (p-value for all variables \leq 0.05). Despite performing frequency matching, the mean age showed significant differences among the three groups; however, age distribution (5-year categories) was not significantly different among the three groups. Among cancer survivors, there were nearly three-fold more women compared to men (3951 vs. 1323). The cancer survivors included 758 gastric, 103 liver, 405 colorectal, 920 breast, 641 cervical, 111 lung, 942 thyroid, 90 prostate, 75 bladder, and 1369 other cancers (Fig. 1 and Table 1). A total of 1756 (33.3%) survivors underwent cancer treatment at the time of the survey. The mean time period from diagnosis was 6.4 years (range, 0–23 years). Among them, about 50% were below the 5 years from the time of diagnosis, and 24% were 10 years and above from the time of diagnosis.

The means of each MeS component in cancer survivors differed significantly from those of the two control groups (Supplemental Table S1). The means of waist circumference, triglyceride level, blood pressure, and glucose level were significantly higher and the mean of HDL significantly lower in cancer survivors compared to those of the CNDZ. In comparison, the means of all metabolic components except HDL were significantly lower and that of HDL higher in cancer survivors compared to the CDZ.

The prevalence of MeS among cancer survivors (25.7%) was significantly higher than that of the CNDZ (18.8%) but lower than that of the CDZ (32.0%) (p < 0.001, Fig. 2). The most prevalent MeS components that met the MeS criteria were blood pressure and waist circumference.

After adjusting for possible confounders (Table 2), the prevalence of MeS was significantly higher in cancer survivors by 1.56-fold (OR = 1.56; 95% confidence interval [CI] = 1.45–1.69) compared to

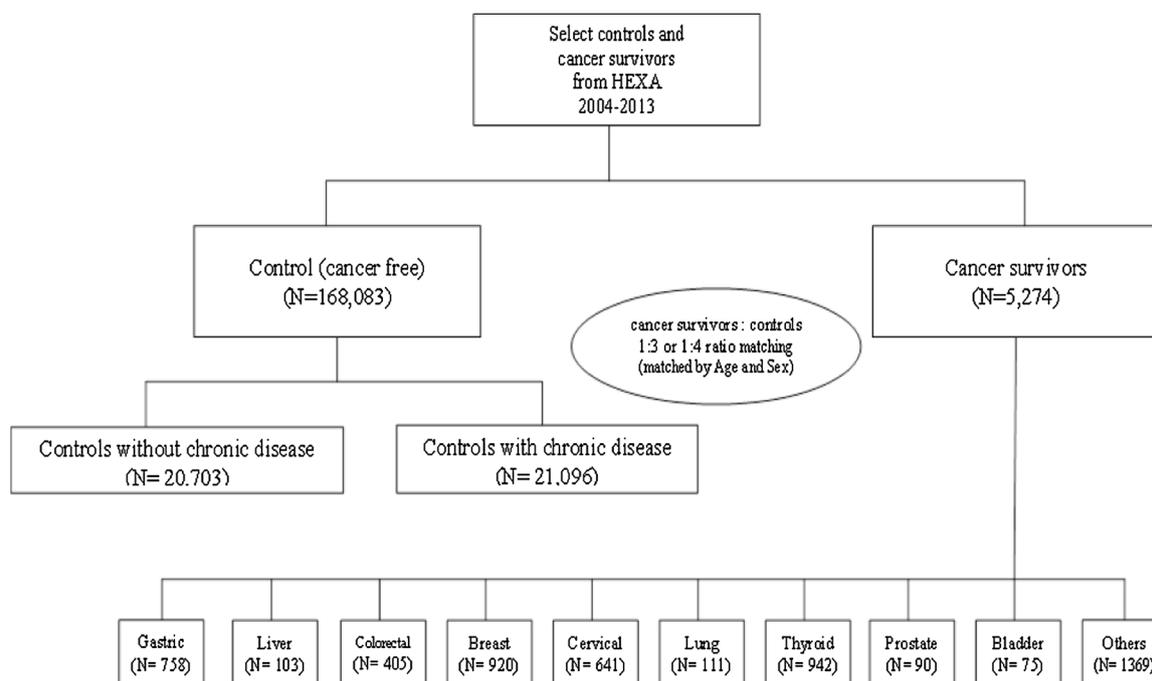


Fig. 1. Flow chart of the patient selection process.

the prevalence in CNDZ. The prevalence of individual MeS components were also significantly higher in cancer survivors compared to those of the CNDZ (waist circumference OR = 1.16, 95% CI = 1.07–1.25; elevated triglyceride OR = 1.23, 95% CI = 1.15–1.33; HDL-cholesterol OR = 1.18; 95% CI = 1.10–1.27; elevated blood pressure OR = 1.50, 95% CI = 1.40–1.60; elevated fasting glucose OR = 1.45, 95% CI = 1.34–1.56). ORs for MeS and its component in CDZ compared to CNDZ were ranged from 1.12 to 2.08. The results of the heterogeneity analysis between cancer survivors and CDZ suggested that the OR of MeS in cancer survivors was significantly lower than that of the CDZ. Thus, although the prevalence of MeS in cancer survivors was higher than that in the CNDZ, it was relatively lower than that in the CDZ (P -heterogeneity < 0.05).

Analysis of the prevalence of MeS in survivors of colorectal, breast, cervical, lung, thyroid, prostate, and bladder cancer showed higher prevalence of MeS compared with that of the CNDZ (OR = 1.63, 1.73, 1.72, 2.11, 1.68, 2.24, and 2.13, respectively; 95% CI = 1.28–2.08, 1.45–2.07, 1.41–2.09, 1.33–3.36, 1.42–1.99, 1.37–3.65, and 1.25–3.61, respectively). The ORs for MeS were lower in gastric and liver cancer survivors, but the difference was not statistically significant. Survivors of breast, cervical, and prostate cancer showed significantly increased ORs for waist circumference compared to the CNDZ (OR range = 1.28–1.89). However, decreased OR for waist circumference was observed in gastric cancer survivors compared to that of the CNDZ (OR = 0.71; 95% CI = 0.57–0.89). Survivors of breast, cervical, and thyroid cancers had a higher prevalence of elevated triglyceride levels than did the CNDZ (OR range = 1.37–1.60); whereas, the same component was lower in gastric and liver cancer survivors (OR = 0.64; CI = 0.52–0.79, OR = 0.43; CI = 0.24–0.79). The prevalence of reduced HDL-cholesterol levels in survivors of lung and thyroid cancers were higher than those of the CNDZ (OR range = 1.48–1.64). An increased prevalence of elevated blood pressure was observed in survivors of colorectal, breast, cervical, thyroid, prostate, and bladder cancers compared to that of the CNDZ (OR range = 1.31–2.16). In addition, except for liver cancer survivors, the prevalence of elevated glucose levels were higher in all cancer type survivors—gastric, colorectal, breast, cervical, lung, thyroid, prostate, and bladder cancer—compared to the CNDZ (OR range = 1.25–2.07) (Table 3). The prevalence of MeS in each type of cancer is shown in Supplemental Table S2.

4. Discussion

In this study, cancer survivors in the community had a 1.56-fold increased association of MeS compared to the CNDZ, corresponding to prevalences of 25.7% and 18.8%, respectively. The prevalence of MeS was lower in cancer survivors than in those with chronic diseases. The prevalence of MeS in cancer survivors reported in previous studies was inconsistent, ranging from 26% to 55% from studies conducted in western countries [9–12] and from 16% to 28.5% from studies conducted in Korea [7,8]. The prevalence of MeS in this study was closer to that reported in a population-based nationwide representative study in Korea [7]. Additionally, cancer survivors in western countries had a 1.6 to 2.1-fold increased prevalence of MeS [9–12], compared to a 1.2-fold increase in Korea [7,8]. The results of the current study showed that the individual MeS components were also significantly higher in cancer survivors compared to those in the CNDZ. The apparent prevalence of increased MeS components among cancer survivors compared to the general population has been reported in other studies, including a higher prevalence of increased waist circumference [12], triglyceride levels [12], and HDL levels [7,12,43], supporting our findings. However, previous studies did not compare MeS in cancer survivors with subjects with chronic disease, based on the potential classification of cancer as a chronic disease. We observed that the prevalence of MeS and each of its components were higher in cancer survivors compared to the prevalence in the CNDZ, but lower than that in the CDZ.

In general, cancer survivors had a higher prevalence of MeS compared to that of the general population, but the prevalence of MeS varied according to cancer type. In gastric cancer survivors, the second-most common cancer in Korea [44], we observed decreased prevalence of MeS, although the difference was not statistically significant. Previous studies have reported significantly decreased ORs for MeS (OR = 0.37, CI = 0.27–0.50; OR = 0.42; CI = 0.20–0.86) in gastric cancer survivors [7,8]. A similar trend was observed for the components of MeS, with decreased OR for increased waist circumference and triglyceride levels in gastric cancer survivors, similar to a study finding in a Korean population [7]. This could be because those who underwent major upper gastrointestinal surgery had higher weight loss [45]. Additionally, liver cancer survivors showed lower prevalence of high triglyceride levels compared with those of the CNDZ. A study showed

Table 1
Baseline characteristics of cancer survivors and matched controls in Korea.

Characteristics ^b	Controls without chronic disease (N = 20,703)	Controls with chronic disease (N = 21,096)	Cancer survivors (N = 5274)	P-value ^a
Age, mean (95% CI)	55.4 (55.3–55.5)	55.8 (55.7–55.9)	55.8 (55.6–56.0)	< 0.001
Age, N (%)				
< 50	5068 (24.5)	5068 (24.0)	1267 (24.0)	0.266
50–54	4436 (21.4)	4436 (21.0)	1109 (21.0)	
55–59	4096 (19.8)	4096 (19.4)	1024 (19.4)	
≥ 60	7103 (34.3)	7496 (35.5)	1874 (35.5)	
Sex, N (%)				
Male	5292 (25.6)	5292 (25.1)	1323 (25.1)	0.499
Female	15411 (74.4)	15,804 (74.9)	3951 (74.9)	
Marital status, N (%)				
Married, cohabitation	17910 (88.0)	18,239 (87.0)	4570 (87.0)	0.005
Divorced, widow, unmarried	2436 (12.0)	2724 (13.0)	681 (13.0)	
Educational attainment, N (%)				
≤ High school	15004 (74.6)	15,946 (76.6)	3859 (74.0)	< 0.001
> College	5111 (25.4)	4873 (23.4)	1353 (26.0)	
Household income, N (%)				
< 2000\$	6398 (37.6)	6889 (40.1)	1800 (39.6)	< 0.001
≥ 2000\$	10,635 (62.4)	10,306 (59.9)	2744 (60.4)	
Employment state, N (%)				
Currently unemployed	10249 (51.4)	11,665 (57.1)	3151 (61.1)	< 0.001
Currently employed	9675 (48.6)	8767 (42.9)	2006 (38.9)	
Self-rated health status, N (%)				
Healthy	9308 (46.0)	6354 (30.5)	1462 (28.0)	< 0.001
Normal-unhealthy	10913 (54.0)	14,502 (69.5)	3767 (72.0)	
Family history of cancer (any type)				
Yes	5215 (25.5)	5952 (28.3)	1894 (36.1)	< 0.001
No	15215 (74.5)	15,050 (71.7)	3353 (63.9)	
Current smoking status, N (%)				
Yes	1818 (8.9)	1692 (8.1)	281 (5.4)	< 0.001
No	18563 (91.1)	19,274 (92.0)	4966 (94.6)	
Current drinking status, N (%)				
Yes	8174 (40.1)	8079 (38.5)	1446 (27.5)	< 0.001
No	12223 (59.9)	12,908 (61.5)	3805 (72.5)	
Exercising, N (%)				
< 150 min/week	12580 (63.9)	12,252 (60.1)	2800 (54.5)	< 0.001
≥ 150 min/week	7103 (36.1)	8119 (39.9)	2333 (45.5)	
BMI, N (%)				
< 23	8996 (43.7)	7693 (36.6)	2309 (44.0)	< 0.001
≥ 23	11568 (56.3)	13,323 (63.4)	2944 (56.0)	
Oral contraceptive usage, N (%)				
Yes	2423 (16.1)	3279 (21.0)	745 (19.0)	< 0.001
No	12641 (83.9)	12,338 (79.0)	3168 (81.0)	
Menopause, N (%)				
Yes	9927 (65.7)	10,893 (69.5)	3112 (79.5)	< 0.001
No	5184 (34.3)	4774 (30.5)	803 (20.5)	
Cancer type ^c (%)				
Gastric			758 (14.0)	
Liver			103 (1.9)	
Colorectal			405 (7.5)	
Breast			920 (17.0)	
Cervical			641 (11.8)	
Lung			111 (2.1)	
Thyroid			942 (17.4)	
Prostate			90 (1.7)	
Bladder			75 (1.4)	
Others			1369 (25.3)	

^a Chi-square test or ANOVA results, P-value in Cancer survivors and Controls (without/with chronic disease); P-value was calculated excluding missing values; CI: confidence intervals.

^b Missing values (N of Cancer survivors, N of Controls without chronic disease, N of Controls with chronic disease): Marital status (23, 357, 133), Educational attainment (62, 588, 277), Household income (730, 3670, 3901), Employment state (117, 779, 664), Self-rated health status (45, 482, 240), Family history of cancer (27, 273, 94), Current smoking status (27, 322, 130), Current drinking status (23, 306, 109), Exercising (141, 1020, 725), BMI (21, 139, 80), Year since diagnosis (120), Status of treatment completion (497). Missing values only in female (N of Cancer survivors, N of Controls without chronic disease, N of Controls with chronic disease): Oral contraceptive usage (43, 347, 187), Menopause (36, 300, 137).

^c Cancer type includes each cancer types in an individual with multiple cancers. Therefore, the sum of these numbers is more than 5274.

decreased hepatic triglyceride levels after hepatectomy [46]. Our study did not collect data on treatment methods in the cancer survivors; thus, we were unable to determine whether the survivors of these two types

of cancers had undergone surgery. However, as surgery is the common treatment for liver [47] and gastric cancers [48], we could assume that gastrointestinal tract or liver surgery may influence our results. A

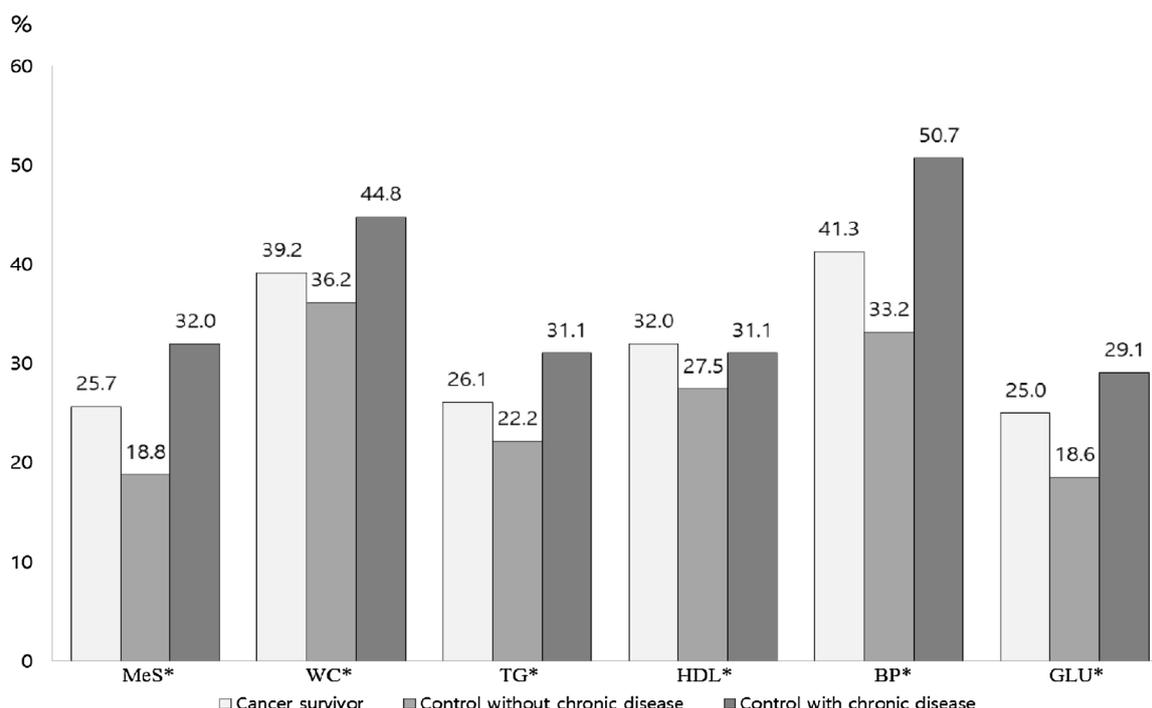


Fig. 2. Prevalence of metabolic components among controls without and with chronic diseases and cancer survivors in Korea. *Statistically significant values < 0.05.

previous studies reporting lower prevalence of MeS in gastric cancer survivors also did not consider treatment modalities [7,8].

We observed a higher prevalence of MeS among colorectal, breast, cervical, lung, thyroid, prostate, and bladder cancer survivors compared to that in the CNDZ. Previous studies also showed a higher prevalence of MeS in colorectal [49], breast [8,12], cervical [50], prostate [8], and bladder cancer survivors [49], supporting our findings on the prevalence of MeS according to cancer type. The increased prevalence of MeS in colorectal cancer survivors may be induced by metabolic abnormalities such as fasting insulin resistance or hyperinsulinemia [51]. Prostate and breast cancer patients are exposed to treatment modalities that are known to increase the prevalence of metabolic abnormalities [52,53]. Additionally, breast cancer survivors may experience MeS due tamoxifen or aromatase inhibitor usage [8]. Although we did not have data regarding the subjects' treatment history, medication therapy can lead to MeS or complications [16,17]; thus, it is likely that cancer treatments influenced the increased prevalence of MeS in cancer survivors.

Similar to our findings, increased prevalence of abdominal obesity, as well as increased triglyceride and HDL levels, were reported in breast cancer survivors [12]. Studies also reported increased prevalence of high HDL levels in breast cancer survivors [7,12], however, the HDL difference was not statistically significant in our study. The fact that a few studies have assessed the prevalence of individual MeS components in site-specific cancer survivors makes our study unique.

This study had several limitations. First, due to its cross-sectional study design, there was the potential for temporal bias and causal relations could not be determined. Considering that MeS is one of the risk factors for cancer development [52], the increased prevalence of MeS in cancer survivors could include MeS which developed before the cancer diagnosis. In addition, the cross-sectional study design may lead to exclusion of cancer survivors with MeS who died before the study, which may skew the results towards favorable outcomes [54]. About one-third of the cancer survivors were under treatment at the time of survey and 50% had been diagnosed within the past five years. The definition of cancer survivors widely includes cancer patients from their diagnosis [55], and study participants were included from local health examination centers and not the oncology unit or cancer care center and were capable of completing the interview and attending routine health check-ups, including blood tests, by themselves. In addition, the prevalence of MeS according treatment status or years from diagnosis did not show statistically significant differences. Thus, we considered all cancer survivors as being capable of returning to the community, irrespective of their treatment status or years since diagnosis and this might not affect the result. Combining several kinds of chronic diseases into one group, CDZ, is a limitation of our study, considering the different associations between each chronic disease with MeS [22–38]. When we compared the prevalence of MeS according to the presence of each chronic disease, it was quite different for different disease types (data not shown). Considering that the definition of chronic disease

Table 2
Increased risk for metabolic syndrome in cancer survivors and those with chronic diseases compared to matched controls without chronic disease in Korea.

Components	Controls without chronic disease Odds ratio (95% confidence intervals) ^a	Controls with chronic disease Odds ratio (95% confidence intervals) ^a	Cancer survivors Odds ratio (95% confidence intervals) ^a	p-heterogeneity
Metabolic syndrome	1	1.95 (1.86–2.05)	1.56 (1.45–1.69)	< 0.001
Waist circumference	1	1.29 (1.23–1.36)	1.16 (1.07–1.25)	< 0.001
Elevated triglyceride	1	1.50 (1.43–1.57)	1.23 (1.15–1.33)	0.002
Reduced HDL-cholesterol	1	1.12 (1.07–1.17)	1.18 (1.10–1.27)	< 0.001
Elevated blood pressure	1	2.08 (2.00–2.17)	1.50 (1.40–1.60)	< 0.001
Elevated fasting glucose	1	1.73 (1.64–1.82)	1.45 (1.34–1.56)	< 0.001

^a Multivariate logistic regression analysis adjusted by age, sex, marital status, education attainment, household income, employment state, self-rated health status, family history of cancer, oral contraceptive usage, menopausal status, BMI, smoking, drinking, exercise status, and carbohydrate intake.

Table 3Risks for metabolic syndrome according to cancer types compared to matched controls without chronic disease in Korea.^d

Var ^c	CNDZ ^a OR ^b	Gastric OR ^b	Liver OR ^b	Colorectal OR ^b	Breast OR ^b	Cervical OR ^b	Lung OR ^b	Thyroid OR ^b	Prostate OR ^b	Bladder OR ^b	Other OR ^b	Multiple OR ^b
MeS	1 (ref)	0.83 (0.65–1.05)	0.77 (0.43–1.38)	1.63 (1.28–2.08)	1.73 (1.45–2.07)	1.72 (1.41–2.09)	2.11 (1.33–3.36)	1.68 (1.42–1.99)	2.24 (1.37–3.65)	2.13 (1.25–3.61)	1.76 (1.53–2.02)	1.54 (1.02–2.34)
WC	1 (ref)	0.71 (0.57–0.89)	0.82 (0.48–1.38)	1.02 (0.79–1.32)	1.28 (1.07–1.52)	1.33 (1.09–1.63)	1.18 (0.71–1.96)	1.03 (0.87–1.21)	1.89 (1.13–3.17)	1.55 (0.89–2.70)	1.34 (1.17–1.55)	0.94 (0.61–1.43)
TG	1 (ref)	0.64 (0.52–0.79)	0.43 (0.24–0.79)	1.18 (0.94–1.48)	1.60 (1.36–1.88)	1.44 (1.19–1.74)	1.17 (0.75–1.83)	1.37 (1.16–1.61)	1.49 (0.94–2.36)	1.23 (0.74–2.07)	1.35 (1.18–1.53)	1.24 (0.83–1.83)
HDL	1 (ref)	0.84 (0.70–1.02)	1.10 (0.68–1.77)	1.05 (0.83–1.34)	1.13 (0.97–1.31)	1.04 (0.87–1.24)	1.64 (1.05–2.54)	1.48 (1.28–1.71)	0.96 (0.54–1.70)	1.03 (0.59–1.83)	1.31 (1.16–1.48)	1.41 (0.98–2.03)
BP	1 (ref)	1.05 (0.89–1.23)	1.03 (0.66–1.60)	1.31 (1.05–1.62)	1.63 (1.40–1.89)	1.57 (1.32–1.87)	1.41 (0.93–2.13)	1.75 (1.52–2.03)	2.16 (1.35–3.45)	2.03 (1.23–3.35)	1.60 (1.42–1.81)	1.40 (0.98–2.00)
GLU	1 (ref)	1.25 (1.05–1.50)	1.48 (0.93–2.36)	1.62 (1.29–2.03)	1.45 (1.21–1.73)	1.56 (1.28–1.90)	1.71 (1.11–2.64)	1.59 (1.35–1.88)	2.07 (1.32–3.25)	1.94 (1.18–3.20)	1.41 (1.23–1.61)	1.80 (1.23–2.63)

The significance of bold value is P-value < 0.05.

^a CNDZ: Controls without chronic disease.^b Odds ratio (95% confidence intervals).^c Variables: MeS = Metabolic Syndrome; WC = waist circumference; TG = elevated triglyceride; HDL = reduced HDL-cholesterol; BP = elevated blood pressure; GLU = elevated fasting glucose.^d Multiple logistic regression analysis was adjusted for age, sex, marital status, education attainment, household income, employment state, self-rated health status, family history of cancer, oral contraceptive usage, menopausal status, BMI, smoking, drinking, exercise status, and carbohydrate intake.

itself includes various types of diseases, including cancer [56], the common feature of which is a medical condition that lasts several months and requires ongoing medical attention [57–59], combining them into a single group (CDZ) would be acceptable despite heterogeneity in the prevalence of MeS. In addition, some of the chronic diseases, including hypertension, diabetes, and dyslipidemia, which we included in the CDZ are components of MeS that were associated with increased MeS prevalence. When we excluded people who reported having all three conditions (hypertension, diabetes, and dyslipidemia), the prevalence of MeS (30.7%) was comparable to the current result (32.0%). All subjects underwent routine health examinations, so might have had more interest and a better understanding of their health status. Thus, the study population may not be representative of the entire Korean population or cancer survivors in Korea. However, the cancer prevalence in our study population was comparable with the results of the Korean Cancer Registry [60]. In addition, despite the limited generalizability, we tried to make the comparability better that of previous studies by selecting cancer survivors and controls from the same source and matching them by age and gender. Differences due to various treatment regimen strategies or stage of cancer could not be analyzed owing to lack of information. Additionally, information bias due to the self-reported questionnaire should be considered in cancer survivor and adjusted variables' definition. Moreover, health behavior changes that occurred after the survey could not be included in the analysis. Despite these limitations, to our knowledge, this is the first study to investigate the prevalence of MeS in cancer survivors who have returned to their normal lives and health status within the general population in the community.

Although cancer survivors showed better health behaviors compared with controls with or without chronic diseases, including reduction in current smoking and drinking and increased physical activity above the recommended level, the results of the current study suggest that cancer survivors are at a higher risk of metabolic syndrome than CNDZ, but their metabolic syndrome prevalence was lower than that of the CDZ. Therefore, MeS in cancer survivors who return to normal life should receive particular attention; furthermore, development of management strategies is required for people with chronic diseases in general. These strategies should include better MeS screening and intervention programs. In addition, cancer diagnosis can potentially be a learning opportunity for patients and encourage them to adopt a healthy lifestyle; thus, education regarding healthy lifestyle practices to prevent metabolic syndrome needs to be provided. Based on the different prevalence of MeS and its components in cancer survivors based

on cancer type, MeS management programs should also be tailored to cancer types, or at least stratified by upper gastrointestinal cancer, liver cancer, and other types of cancer. Additional prospective studies investigating the prevalence of MeS throughout the course of cancer survivor care plans may offer data to develop better interventions in these subjects.

Conflict of interest statement

The authors report no conflicts of interest.

Funding

This study was supported by a Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Science, ICT and Future Planning (NRF-2016R1C1B1013621).

Authorship contribution statement

MK, I-HK, MKL, YK, and BP conceived and designed the study. BP acquired and collated the data. MK analyzed the data. All authors drafted and critically revised the manuscript for important intellectual content and gave final approval of the version to be published.

Acknowledgments

This study used data from the Korean Genome Analysis Project (4845-301), the Korean Genome and Epidemiology Study (4851-302), and the Korea Biobank Project (4851-307, KBP-2014-041), which were supported by the Korea Centers for Disease Control and Prevention, Republic of Korea.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.canep.2018.12.006>.

References

- [1] J. Ferlay, I. Soerjomataram, R. Dikshit, S. Eser, C. Mathers, M. Rebelo, et al., Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012, *Int. J. Cancer* 136 (5) (2015) E359–86.

- [2] Society AC, Cancer Treatment and Survivorship Facts & Figures 2014–2015, American Cancer Society Atlanta, 2014.
- [3] D.W. Shin, J.H. Nam, Y.C. Kwon, S.Y. Park, D.S. Bae, C.T. Park, et al., Comorbidity in disease-free survivors of cervical cancer compared with the general female population, *Oncology* 74 (3–4) (2008) 207–215.
- [4] A.E. Kero, L.S. Jarvela, M. Arola, N. Malila, L.M. Madanat-Harjuoja, J. Matomaki, et al., Late mortality among 5-year survivors of early onset cancer: a population-based register study, *Int. J. Cancer* 136 (7) (2015) 1655–1664.
- [5] H.S. Jung, S.K. Myung, B.S. Kim, H.G. Seo, Metabolic syndrome in adult cancer survivors: a meta-analysis, *Diabetes Res. Clin. Pract.* 95 (2) (2012) 275–282.
- [6] S.M. Grundy, Metabolic syndrome: a multiplex cardiovascular risk factor, *J. Clin. Endocrinol. Metab.* 92 (2) (2007) 399–404.
- [7] J.Y. Lee, N.H. Park, Y.S. Song, S.M. Park, H.W. Lee, K.H. Kim, et al., Prevalence of the metabolic syndrome and associated factors in Korean cancer survivors, *Asian Pac. J. Cancer Prev.* 14 (3) (2013) 1773–1780.
- [8] J.Y. Shin, Y.H. Choi, Y.M. Song, Metabolic syndrome in Korean cancer survivors and family members: a study in a health promotion center, *Nutr. Cancer* 67 (7) (2015) 1075–1082.
- [9] H.S. Haugnes, N. Aass, S.D. Fossa, O. Dahl, O. Klepp, E.A. Wist, et al., Components of the metabolic syndrome in long-term survivors of testicular cancer, *Ann. Oncol.* 18 (2) (2007) 241–248.
- [10] M. Braga-Basaria, A.S. Dobs, D.C. Muller, M.A. Carducci, M. John, J. Egan, et al., Metabolic syndrome in men with prostate cancer undergoing long-term androgen-deprivation therapy, *J. Clin. Oncol.* 24 (24) (2006) 3979–3983.
- [11] A.H. Liavaag, S. Tonstad, A.H. Pripp, C. Trope, A. Dorum, Prevalence and determinants of metabolic syndrome and elevated framingham risk score in epithelial ovarian cancer survivors: a controlled observational study, *Int. J. Gynecol. Cancer* 19 (4) (2009) 634–640.
- [12] C. Agnoli, F. Berrino, C.A. Abagnato, P. Muti, S. Panico, P. Crosignani, et al., Metabolic syndrome and postmenopausal breast cancer in the ORDET cohort: a nested case-control study, *Nutr. Metab. Cardiovasc. Dis.* 20 (1) (2010) 41–48.
- [13] K. la Cour, M.P. Cutchin, Developing community based rehabilitation for cancer survivors: organizing for coordination and coherence in practice, *BMC Health Serv. Res.* 13 (1) (2013) 339.
- [14] P.A. Ganz, Editor Late Effects of Cancer and Its Treatment. Seminars in Oncology Nursing, Elsevier, 2001.
- [15] K.H. Kim, Y.Y. Cho, D.W. Shin, J.H. Lee, Y.J. Ko, S.M. Park, Comparison of physical and mental health status between cancer survivors and the general population: a Korean population-based survey (KNHANES II-IV), *Support Care Cancer* 21 (12) (2013) 3471–3481.
- [16] P.J. Saylor, M.R. Smith, Metabolic complications of androgen deprivation therapy for prostate cancer, *J. Urol.* 189 (1 Suppl) (2013) S34–S42 discussion S3–4.
- [17] A.J. Redig, H.G. Munshi, Metabolic syndrome after hormone-modifying therapy: risks associated with antineoplastic therapy, *Oncology (Williston Park)* 24 (9) (2010) 839–844.
- [18] J.L. Phillips, D.C. Currow, Cancer as a chronic disease, *Collegian* 17 (2) (2010) 47–50.
- [19] J.Q. Tritter, M. Calnan, Cancer as a chronic illness? Reconsidering categorization and exploring experience, *Eur. J. Cancer Care (Engl.)* 11 (3) (2002) 161–165.
- [20] D.C. Witter, J. LeBas, Cancer as a chronic disease, *Oncology* 53 (4) (2008) 1–3.
- [21] K.N. Society, Food Composition Tables in Recommended Dietary Allowances for Koreans, 7th edition, Joong Ang Moon Wha Publishing Co., Seoul, 2011.
- [22] J.K. Ninomiya, G. L'Italien, M.H. Criqui, J.L. Whyte, A. Gamst, R.S. Chen, Association of the metabolic syndrome with history of myocardial infarction and stroke in the Third National Health and Nutrition Examination Survey, *Circulation* 109 (1) (2004) 42–46.
- [23] N.T. Nguyen, C.P. Magno, K.T. Lane, M.W. Hinojosa, J.S. Lane, Association of hypertension, diabetes, dyslipidemia, and metabolic syndrome with obesity: findings from the National Health and Nutrition Examination Survey, 1999 to 2004, *J. Am. Coll. Surg.* 207 (6) (2008) 928–934.
- [24] N. Koren-Morag, U. Goldbourt, D. Tanne, Relation between the metabolic syndrome and ischemic stroke or transient ischemic attack a prospective cohort study in patients with atherosclerotic cardiovascular disease, *Stroke* 36 (7) (2005) 1366–1371.
- [25] S. Watanabe, M. Hojo, A. Nagahara, Metabolic syndrome and gastrointestinal diseases, *J. Gastroenterol.* 42 (4) (2007) 267–274.
- [26] S. Tal, E. Melzer, T. Chsherbakov, S. Malnick, Metabolic syndrome is associated with increased prevalence of advanced colorectal polyps, *J. Nutr. Health Aging* 18 (1) (2014) 22–25.
- [27] G. Marchesini, E. Bugianesi, G. Forlani, F. Cerrelli, M. Lenzi, R. Manini, et al., Nonalcoholic fatty liver, steatohepatitis, and the metabolic syndrome, *Hepatology* 37 (4) (2003) 917–923.
- [28] G.L. Wong, V.W. Wong, P.C. Choi, A.W. Chan, A.M. Chim, K.K. Yiu, et al., Metabolic syndrome increases the risk of liver cirrhosis in chronic hepatitis B, *Gut* 58 (1) (2009) 111–117.
- [29] N. Ata, M. Kucukazman, B. Yavuz, H. Bulus, K. Dal, D. Taner Ertugrul, et al., The metabolic syndrome is associated with complicated gallstone disease, *Can. J. Gastroenterol.* 25 (5) (2011) 274.
- [30] N. Leone, D. Courbon, F. Thomas, K. Bean, B. Jégo, B. Leynaert, et al., Lung function impairment and metabolic syndrome: the critical role of abdominal obesity, *Am. J. Respir. Crit. Care Med.* 179 (6) (2009) 509–516.
- [31] A.C. Waring, N. Rodondi, S. Harrison, A.M. Kanaya, E.M. Simonsick, I. Miljkovic, et al., Thyroid function and prevalent and incident metabolic syndrome in older adults: the health, ageing and body composition study, *Clin. Endocrinol.* 76 (6) (2012) 911–918.
- [32] H.K. Choi, E.S. Ford, C. Li, G. Curhan, Prevalence of the metabolic syndrome in patients with gout: the Third National Health and Nutrition Examination Survey, *Arthritis Care Res.* 57 (1) (2007) 109–115.
- [33] C.P. Chung, A. Oeser, J.F. Solus, I. Avalos, T. Gebretsadik, A. Shintani, et al., Prevalence of the metabolic syndrome is increased in rheumatoid arthritis and is associated with coronary atherosclerosis, *Atherosclerosis* 196 (2) (2008) 756–763.
- [34] P.A. Newman-Casey, N. Talwar, B. Nan, D.C. Musch, J.D. Stein, The relationship between components of metabolic syndrome and open-angle glaucoma, *Ophthalmology* 118 (7) (2011) 1318–1326.
- [35] A. Paunksnis, F. Bojarskiene, A. Cimbaldas, L. Cerniauskiene, D. Luksiene, A. Tamosiunas, Relation between cataract and metabolic syndrome and its components, *Eur. J. Ophthalmol.* 17 (4) (2007) 605–614.
- [36] P.H. Dessein, M. Tobias, M.G. Veller, Metabolic syndrome and subclinical atherosclerosis in rheumatoid arthritis, *J. Rheumatol.* 33 (12) (2006) 2425–2432.
- [37] D.L. Foley, K.I. Morley, P.A. Madden, A.C. Heath, J.B. Whitfield, N.G. Martin, Major depression and the metabolic syndrome, *Twin Res. Hum. Genet.* 13 (04) (2010) 347–358.
- [38] D.-K. Hwang, H.-J. Choi, The relationship between low bone mass and metabolic syndrome in Korean women, *Osteoporos. Int.* 21 (3) (2010) 425–431.
- [39] S.M. Grundy, J.I. Cleeman, S.R. Daniels, K.A. Donato, R.H. Eckel, B.A. Franklin, et al., Diagnosis and management of the metabolic syndrome an American Heart Association/National Heart, Lung, and Blood Institute scientific statement, *Circulation* 112 (17) (2005) 2735–2752.
- [40] L.H. Kushi, C. Doyle, M. McCullough, C.L. Rock, W. Demark-Wahnefried, E.V. Bandera, et al., American cancer society guidelines on nutrition and physical activity for cancer prevention, *CA Cancer J. Clin.* 62 (1) (2012) 30–67.
- [41] Association AD, Standards of medical care in diabetes—2015 abridged for primary care providers, *Clin. Diabetes* 33 (2) (2015) 97–111.
- [42] Y.W. Park, S. Zhu, L. Palaniappan, S. Heshka, M.R. Carnethon, S.B. Heymsfield, The metabolic syndrome: prevalence and associated risk factor findings in the US population from the Third National Health and Nutrition Examination Survey, 1988–1994, *Arch. Intern. Med.* 163 (4) (2003) 427–436.
- [43] K.K. Talvensaaari, M. Lanning, P. Tapanainen, M. Knip, Long-term survivors of childhood cancer have an increased risk of manifesting the metabolic syndrome, *J. Clin. Endocrinol. Metab.* 81 (8) (1996) 3051–3055.
- [44] C.M. Oh, Y.J. Won, K.W. Jung, H.J. Kong, H. Cho, J.K. Lee, et al., Cancer statistics in Korea: incidence, mortality, survival and prevalence in 2013, *Cancer Res. Treat.* 48 (2) (2016) 436–450.
- [45] S. Carey, D. Storey, A.V. Biankin, D. Martin, J. Young, M. Allman-Farinelli, Long term nutritional status and quality of life following major upper gastrointestinal surgery—a cross-sectional study, *Clin. Nutr.* 30 (6) (2011) 774–779.
- [46] M. Kohjima, T.H. Tsai, B.C. Tackett, S. Thevananther, L. Li, B.H. Chang, et al., Delayed liver regeneration after partial hepatectomy in adipose differentiation related protein-null mice, *J. Hepatol.* 59 (6) (2013) 1246–1254.
- [47] A.B. Benson 3rd, T.A. Abrams, E. Ben-Josef, P.M. Bloomston, J.F. Botha, B.M. Clary, et al., NCCN clinical practice guidelines in oncology: hepatobiliary cancers, *J. Natl. Compr. Cancer Netw.* 7 (4) (2009) 350–391.
- [48] M. Orditura, G. Galizia, V. Forza, V. Gambardella, A. Fazio, M.M. Laterza, et al., Treatment of gastric cancer, *World J. Gastroenterol.* 20 (7) (2014) 1635–1649.
- [49] K. Esposito, P. Chiodini, A. Colao, A. Lenzi, D. Giugliano, Metabolic syndrome and risk of cancer: a systematic review and meta-analysis, *Diabetes Care* 35 (11) (2012) 2402–2411.
- [50] E.K. Penaranda, N. Shokar, M. Ortiz, Relationship between metabolic syndrome and history of cervical cancer among a US national population, *ISRN Oncol.* 2013 (2013).
- [51] R.L. Ahmed, K.H. Schmitz, K.E. Anderson, W.D. Rosamond, A.R. Folsom, The metabolic syndrome and risk of incident colorectal cancer, *Cancer* 107 (1) (2006) 28–36.
- [52] E.C. de Haas, S.F. Oosting, J.D. Lefrandt, B.H. Wolffenbuttel, D.T. Sleijfer, J.A. Gietema, The metabolic syndrome in cancer survivors, *Lancet Oncol.* 11 (2) (2010) 193–203.
- [53] M.J. Hoening, A. Botma, B.M. Aleman, M.H. Baaijens, H. Bartelink, J.G. Klijn, et al., Long-term risk of cardiovascular disease in 10-year survivors of breast cancer, *J. Natl. Cancer Inst.* 99 (5) (2007) 365–375.
- [54] M.D. Carlson, R.S. Morrison, Study design, precision, and validity in observational studies, *J. Palliat. Med.* 12 (1) (2009) 77–82.
- [55] C.S. Denlinger, R.W. Carlson, M. Are, K.S. Baker, E. Davis, S.B. Edge, et al., Survivorship: introduction and definition. Clinical practice guidelines in oncology, *J. Natl. Compr. Cancer Netw.* 12 (1) (2014) 34–45.
- [56] A.P. Wilper, S. Woolhandler, K.E. Lasser, D. McCormick, D.H. Bor, D.U. Himmelstein, A national study of chronic disease prevalence and access to care in uninsured U.S. adults, *Ann. Intern. Med.* 149 (3) (2008) 170–176.
- [57] MedicineNet, Definition of Chronic Disease, Available from: (2016) <http://www.medicinenet.com/script/main/art.asp?articlekey=33490>.
- [58] CDC, Chronic Disease Overview, Available from: (2016) <http://www.cdc.gov/chronicdisease/overview/index.htm>.
- [59] G. Warshaw, Introduction: advances and challenges in care of older people with chronic illness, *Generations* 30 (3) (2006) 5–10.
- [60] K.W. Jung, Y.J. Won, C.M. Oh, H.J. Kong, D.H. Lee, K.H. Lee, Cancer statistics in Korea: incidence, mortality, survival, and prevalence in 2014, *Cancer Res. Treat.* 49 (2) (2017) 292–305.