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Associations of cardiovascular risk factors with survival outcomes in a cancer registration

Findings from the KUMAMON registry

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Abstract

Although the relationship between cardiovascular diseases and malignant diseases has recently attracted attention, the associations of cardiovascular risk factors and clinical outcomes in cancer patients remain to be elucidated. We performed a retrospective, observational study that explored the clinical outcomes of patients with cancer or with a history of cancer.

We enrolled 30,706 consecutive adult cancer patients from Kumamoto University Hospital. We investigated mortality and morbidity, including cardiovascular conditions (dyslipidemia [DL]/diabetes mellitus [DM]/hypertension [HT]). The primary endpoint was all-cause mortality.

Of the enrolled patients, 9032 patients (29.4%) died within the follow-up period. The Kaplan–Meier analysis demonstrated that in the groups classified according to the number of DL/DM/HT (LDH) factors, the LDH1 and LDH2 groups had a significantly higher probability of the primary endpoint than the LDH0 group ($P < .001$ and $P < .001$, respectively), whereas there were no significant differences between the LDH0 group and LDH3 group ($P = .963$). Univariate Cox proportional hazards regression analyses of mortality complemented by the multiple imputation method including various factors demonstrated that the presence of DL in cancer patients was a significant negative predictor of mortality (hazard ratio = 0.79, $P < .01$).

The all-cause mortality rate did not always increase as the number of LDH factors increased. The present study revealed that the presence of DL is a negative risk factor for all-cause mortality in cancer patients.

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Abbreviations: DL = dyslipidemia, DM = diabetes mellitus, HDL = high-density lipoprotein, HR = hazard ratio, HT = hypertension, ICD = International Classification of Diseases, LDH = DL/DM/HT, LDL = low-density lipoprotein, T-Chol = total cholesterol, TG = triglyceride.

Keywords: diabetes, hyperlipidemia, hypertension, outcomes

1. Introduction

Cancer treatment has made great progress, and in addition to traditional surgery, chemotherapy, and radiation therapy, molecular-targeted therapies[1] and immune checkpoint inhibitors[2] that make use of the latest advancements in molecular biology have recently been developed. These treatments greatly contribute to improving the prognosis of cancer patients. On the other hand, these cancer treatments place a heavy burden on the cardiovascular system of cancer patients and sometimes cause fatal cardiovascular complications. Therefore, the ultimate goal of cardio-oncology is to manage the risk factors and underlying diseases of the cardiovascular system in cancer-bearing patients so that they can receive adequate cancer treatment and so that cancer survivors can maintain their quality of life without the onset of cardiovascular diseases.[3] Several conventional risk factors and underlying pathophysiological mechanisms linked with cardiovascular disease are associated with an increased risk for specific types of cancers,[4] these conventional risk factors are well known as risk factors for cardiotoxicity.[5] The associations between cardiovascular risk factors and mortality in the cancer population have been reported[6,7]; the relationships between these risk factors and malignant diseases have been comprehensively reviewed.[8] However, cardiovascular conditions in these reports were identified using *International Classification of Diseases* (*ICD*), the actual situation in associations of cardiovascular risk factors and clinical outcomes in cancer patients remain to be elucidated.

In the present study, we investigated the relationship between conventional cardiovascular risk factors and mortality in cancer patients.

2. Methods

The present study was a prospective, single-center, observational study that explored clinical outcomes in patients with cancer or with a history of cancer.

2.1. Ethical consideration

All procedures were conducted in accordance with the Declaration of Helsinki and its amendments. The study protocol was approved by the institutional review board of Kumamoto University (approval number, Rinri 1858). This study is registered at the University Hospital Medical Information Network Clinical Trials Registry (UMIN000047554).

Opt-out materials are available at: https://kumadai-junnai.com/wp-content/uploads/kcancer.pdf

2.2. Study subjects

The KUMAMON (Kumamoto Malignancy Mortality and Morbidity) registry was a multicenter, prospective, community-based observational registry study conducted throughout Kumamoto Prefecture. The Kumamoto Prefecture is located southwest of Tokyo and has a population of approximately 1.8 million people.[9,10] The KUMAMON registry included 167,439 cancer cases in the Kumamoto Prefecture (21 hospitals [details are described in the Appendix, http://links.lww.com/MD/G494]) between January 2007 and December 2018. The present study included 34,664 consecutive cancer patients at Kumamoto University Hospital from the KUMAMON registry. We excluded 3522 duplicated patients. Of 31,142 cancer patients, 436 patients aged <20 years were excluded because this study aimed to observe the effects of lifestyle diseases on malignant diseases. The remaining 30,706 adult cancer patients were enrolled (Fig. 1). The exact observational end date was 30 June 2020. All data were collected and aggregated by a trained research team at the Division of Cardiovascular Disease of Kumamoto University.

2.3. Clinical parameters

Baseline demographic data, cardiovascular risk factors, and medications on enrollment were documented. Hypertension

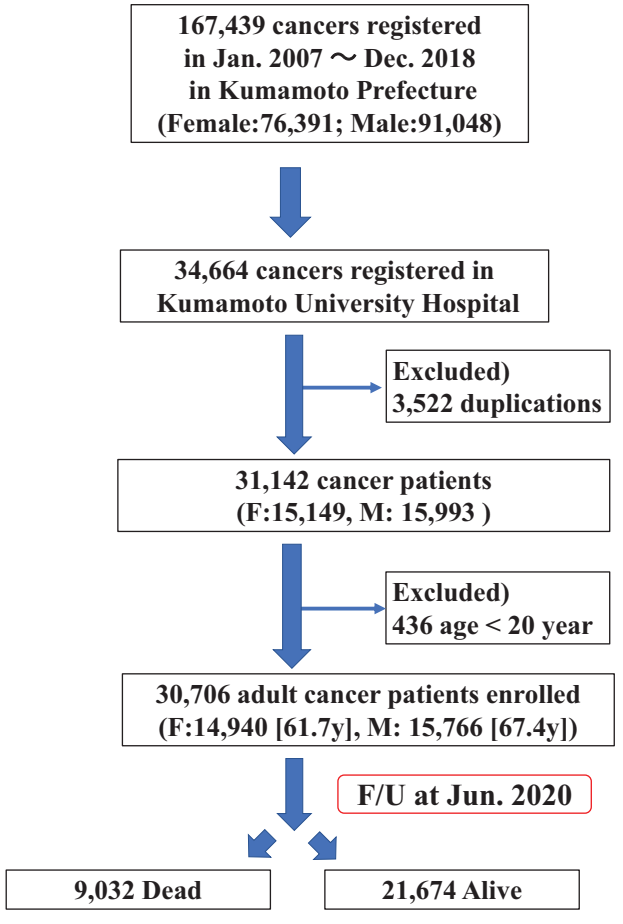

Figure 1. Study flowchart. F = female, F/U = follow up, M = male.

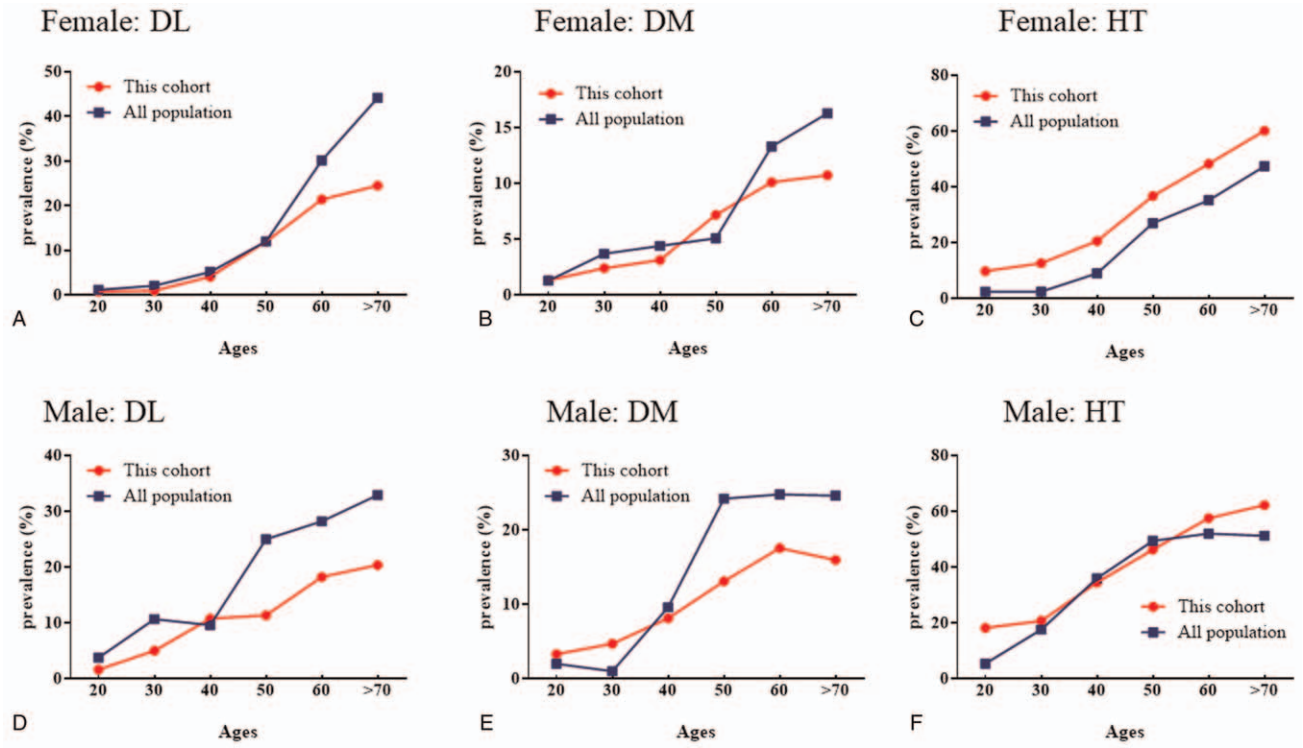

Figure 2. The prevalence of cardiovascular conditions in each age group. (A) dyslipidemia in females; (B) diabetes mellitus in females; (C) hypertension in females. (D) dyslipidemia in males; (E) diabetes mellitus in males; (F) hypertension in males.

(HT) was defined as blood pressure >140/90 mmHg or taking antihypertensive medication, as previously described.[11–13] Diabetes mellitus (DM) was defined as the presence of symptoms of diabetes and a casual plasma glucose concentration ≥200 mg/dL, a fasting plasma glucose concentration ≥126 mg/dL, and a 2-hour plasma glucose concentration ≥200 mg/dL on the oral glucose tolerance test (75 g), or taking medication for DM. Dyslipidemia (DL) was defined as a low-density lipoprotein (LDL) cholesterol concentration ≥140 mg/dL (≥3.63 mmol/L), a high-density lipoprotein (HDL) cholesterol concentration <40 mg/dL (1.04 mmol/L), or a triglyceride (TG) concentration ≥150 mg/dL (≥1.7 mmol/L). Blood samples were obtained under stable and fasting conditions in the early morning. Moreover, we calculated how many risk factors each patient had and expressed the results as DL/DM/HT (LDH) numbers.

2.4. Follow-up

After enrollment, the patients were followed up prospectively at the outpatient clinics until an endpoint occurred. The primary endpoint was all-cause death. The endpoint was ascertained from a review of the medical records and confirmed by direct contact with the patients, their families, their physicians, or an annual telephone interview conducted with each patient.

2.5. Statistical analysis

The Shapiro–Wilk test was used to assess the normality of the distribution of the continuous data. Continuous variables with a normal distribution are expressed as the mean ± standard deviation, whereas those with skewed distributions are expressed as the median value with an interquartile range. Categorical data are presented as numbers or percentages. Differences between two groups were tested using Fisher exact test or the χ^2 test for categorical variables and the Mann–Whitney U test for continuous variables, as appropriate. We used the Kaplan–Meier method to estimate the primary endpoint probabilities and the log-rank test to compare the distributions of survival times among groups. Cox proportional hazards models were used to calculate the hazard ratios (HRs) (Fig. 2). The missing values of the clinical parameters were supplemented by the multiple imputation method based on a previous report.[14] In brief, multiple imputation was used to handle missing data and was performed with 20 imputed datasets generated by the fully conditional specification method. The results across 20 imputed datasets were combined using Rubin rules.[15] A P value <.05 was considered to denote statistical significance. Statistical analyses were performed using SPSS version 26 (IBM Inc., Armonk, NY).

3. Results

3.1. Patient characteristics and malignant disease incidence

Of the 30,706 enrolled patients, 9032 patients (29.4%) died within the follow-up period. Accordingly, the patients were divided into 2 groups: the death group and the survival group. Table 1 shows the baseline characteristics of patients in the death group (n = 9032) and the survival group (n = 21,674). Among the

Table 1

Baseline patient characteristics at the time of enrolment.

	Overall (n = 30,706)	Death (n = 9032)	Survival (n = 21,674)	*P*
Age, y	67 (56–76)	71 (62–79)	65 (54–74)	<.001
Male (%)	15,766 (51.3)	5764 (63.8)	10,002 (46.1)	<.001
BMI, kg/m^2	22.6 (20.3–25.1)	21.8 (19.5–24.3)	22.8 (20.6–25.3)	<.001
BSA, m^2	1.6 (1.5–1.7)	1.6 (1.5–1.7)	1.6 (1.5–1.7)	<.001
F/U period, mo	51 (25–93)	16 (6–34)	70 (42–108)	<.001
Dyslipidemia (%)	5206 (17.0)	1287 (14.2)	3939 (18.2)	<.001
Diabetes mellitus (%)	3620 (11.8)	1206 (13.4)	2414 (11.1)	<.001
Hypertension (%)	15,222 (49.6)	5035 (55.7)	10,187 (47.0)	<.001
No. of L/D/H	1 (0–1)	1 (0–1)	1 (0–1)	<.001
Stage				
0 (%)	2217 (7.2)	125 (1.4)	2092 (9.7)	<.001
I (%)	9726 (31.7)	1574 (17.4)	8152 (37.6)	<.001
II (%)	4269 (13.9)	1063 (11.8)	3206 (14.7)	<.001
III (%)	2787 (9.1)	1151 (12.7)	1636 (7.5)	<.001
IV (%)	4343 (14.1)	2520 (27.9)	1823 (8.4)	<.001
Not available (%)	967 (3.1)	78 (0.9)	889 (4.1)	<.001
Unknown (%)	6397 (20.8)	2521 (27.9)	3876 (17.9)	<.001
Stage (mean)	1 (1–3)	3 (1–4)	1 (1–2)	<.001
Procedure(s)*	18,198 (59.3)	3398 (37.6)	14,800 (68.3)	<.001
Surgery	13,849 (45.1)	2837 (31.4)	10,652 (49.1)	<.001
Video-assisted	3328 (10.8)	323 (3.6)	3005 (13.9)	<.001
Endoscopic	1552 (5.1)	275 (3.0)	1277 (5.9)	<.001
Radiation	4533 (14.8)	1742 (19.3)	2791 (12.8)	<.001
Chemotherapy	9228 (30.1)	4170 (19.2)	5058 (23.3)	<.001
Endocrine therapy	1766 (5.8)	241 (2.7)	1525 (7.0)	<.001
WBC	6.1 [4.8–7.7)	6.2 (4.6–8.2)	6.1 (4.9–7.6)	<.001
RBC	4.2 (3.8–4.6)	3.9 (3.4–4.3)	4.3 (4.0–4.7)	<.001
Hemoglobin, g/dL	13.0 (11.6–14.2)	12.0 (10.4–13.5)	13.3 (12.1–14.4)	<.001
Total protein	7.0 (6.5–7.4)	6.8 (6.2–7.3)	7.1 (6.7–7.4)	<.001
Albumin, g/dL	4.0 (3.6–4.0)	3.6 (3.1–4.1)	4.2 (3.8–4.4)	<.001
AST	22 (17–29)	24 (18–38)	21 (17–27)	<.001
ALT	17 (12–27)	18 (12–32)	17 (12–25)	<.001
T-Bil	0.7 (0.5–0.9)	0.7 (0.5–1.0)	0.7 (0.5–0.9)	<.001
BUN, mg/dL	14.1 (11.3–17.8)	15.1 (11.9–21.1)	13.8 (11.1–17.1)	<.001
Creatinine, mg/dL	0.7 (0.6–0.9)	0.8 (0.6–0.9)	0.7 (0.6–0.9)	<.001
Uric acid, mg/dL	5.1 (4.1–6.2)	5.2 (4.0–6.4)	5.1 (4.1–6.1)	<.001
Serum sodium	140 (138–141)	139 (137–141)	140 (139–142)	<.001
serum potassium	4.3 (4.0–4.5)	4.3 (4.0–4.6)	4.2 (4.0–4.5)	<.001
Serum chlorine	106 (104–107)	105 (102–107)	106 (104–107)	<.001
Total-cholesterol, mg/dL	188 (161–215)	173 (144–202)	193 (168–219)	<.001
LDL-cholesterol, mg/dL	109 (87–133)	99 (77–123)	113 (92–136)	<.001
HDL-cholesterol, mg/dL	58 (46–72)	51 (40–65)	60 (48–74)	<.001
TG, mg/dL	101 (73–144)	95 (71–135)	103 (74–148)	<.001
CRP	0.13 (0.05–0.75)	0.43 (0.10–2.29)	0.09 (0.04–0.39)	<.001
HbA1c	5.8 (5.5–6.2)	5.8 (5.4–6.4)	5.8 (5.5–6.2)	<.001
BS	103 (94–119)	106 (94–128)	103 (94–117)	<.001
BNP	28.2 (13.1–64.1)	45.4 (20.0–109.9)	23.4 (11.3–51.1)	<.001
Hs-TnT	0.01 (0.01–0.02)	0.01 (0.00–0.01)	0.01 (0.01–0.02)	.50

Values are represented as median (25th–75th percentile ranges) or n (%).

* Overlaps possible.

ALT = alanine aminotransferase level, AST = aspartate aminotransferase level, BMI = body mass index, BNP = brain natriuretic peptide level, BS = blood sugar level, BSA = body surface area, CRP = C-reactive protein level, F/U = follow up, HbA1c = hemoglobin A1c level, HDL = high-density lipoprotein cholesterol concentration, Hs-TnT = high-sensitivity-troponin T level, L/D/H = dyslipidemia/diabetes/hypertension factors, LDL = low-density lipoprotein cholesterol concentration, RBC = red blood cell count, TG = triglycerides concentration, WBC = white blood cell count.

clinical features examined, age, sex, body surface area, presence of DM, presence of HT, LDH number, proportion of stage III, proportion of stage IV, mean cancer stage, proportion of radiation therapy, white blood cell count, and aspartate aminotransferase, alanine aminotransferase, total bilirubin, blood urea nitrogen, serum creatinine, uric acid, serum potassium, C-reactive protein, hemoglobin A1c, plasma glucose, and brain natriuretic peptide levels were significantly higher in the death group than in the survival group. Conversely, body mass index, follow-up periods, proportion of stage 0, proportion of stage I, proportion of stage II, proportion of procedure(s) [surgery, endoscopic surgery, and video-assisted surgery (overlaps possible)], proportion of surgery, proportion of video-assisted surgery, proportion of endoscopic surgery, proportion of chemotherapy, proportion of endocrine therapy, red blood cell count, and hemoglobin, total protein, albumin, serum sodium,

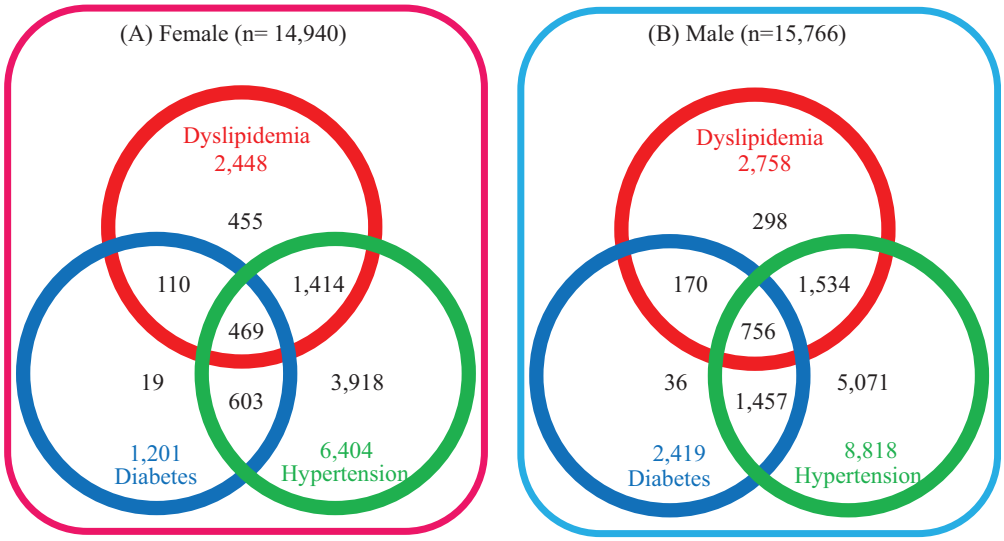

Figure 3. Venn diagrams showing the number of patients with ≥1 cardiovascular conditions. (A) Females; (B) Males.

serum chloride, total cholesterol (T-Chol), LDL cholesterol, HDL cholesterol and TG levels were significantly lower in the death group than in the survival group. The distributions of ages in all 31,142 cancer patients are shown in Supplemental Figure 1, http://links.lww.com/MD/G495 (A: females, B: males). The top three most common malignant diseases in female patients were breast, uterus, and skin cancers (Supplemental Figure 2A, http://links.lww.com/MD/G496), and the top three in male patients were lung, liver and prostate cancers (Supplemental Figure 2B, http://links.lww.com/MD/G496).

3.2. The prevalence of cardiovascular conditions in cancer patients

Figure 3 demonstrates the prevalence of cardiovascular conditions (DL/DM/HT) for each age group based on the National Health and Nutrition Survey Report issued by the Ministry of Health, Labor and Welfare.[16] It was revealed that the older the age group was, the greater the prevalence of cardiovascular conditions in cancer patients, similar to that in the overall population. Figure 4 displays Venn diagrams showing the number of patients with ≥1 cardiovascular conditions.

3.3. Effect of LDH factors on mortality

Figure 5 shows the mortality of each LDH factor. LDH1 consists of 753 DL only, 55 DM only, and 8989 HT only patients. LDH2 consists of 2060 DM plus HT, 2948 DL plus HT, and 280 DL plus DM patients. As shown in Figure 5, the all-cause mortality rate did not always increase as the number of factors increased. The Kaplan–Meier analysis demonstrated a significantly higher probability of the primary endpoint in the LDH1 and LDH2

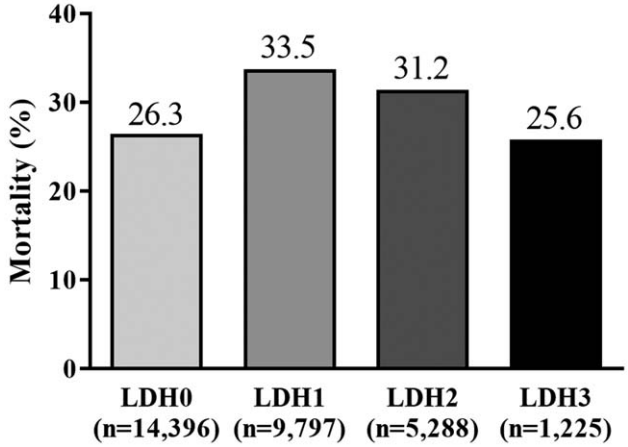

Figure 4. The all-cause mortality rate and the number of dyslipidemia diabetes hypertension (LDH) factors.

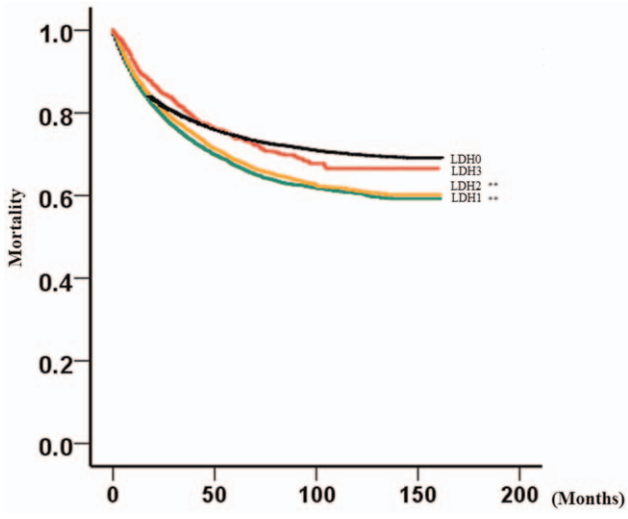

Figure 5. Kaplan–Meier curves for survival rate during the follow-up period among four groups: the number of dyslipidemia-diabetes-hypertension (LDH) factors. $^{**}P < .01$ vs LDH0.

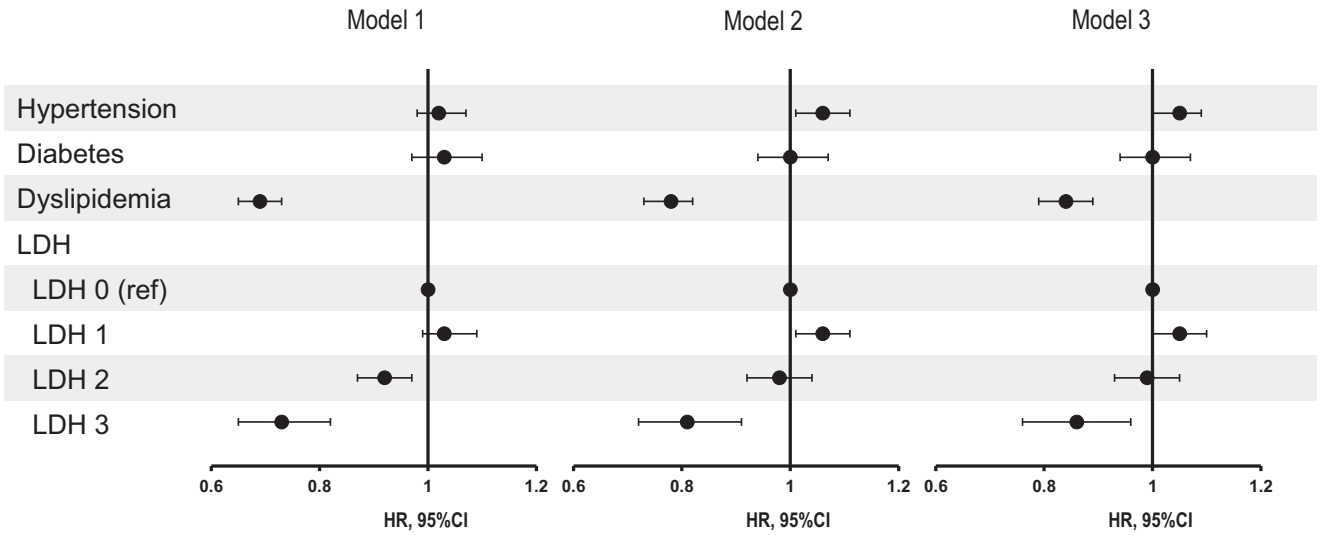

Figure 6. Forest plot of survival by the prevalence of cardiovascular conditions and the number of dyslipidemia-diabetes-hypertension (LDH) factors. Model 1was adjusted by age and sex. Model 2 was adjusted by Model 1 + cancer stage, procedure(s), radiation, chemotherapy and endocrine therapy. Model 3 was adjusted by Model 2 + albumin, hemoglobin, creatinine, and C-reactive protein level.

groups than in the LDH0 group ($P < .001$ and $P < .001$, respectively), whereas there were no significant differences between the LDH0 group and LDH3 group ($P = .963$; Fig. 6).

3.4. Predictors of mortality according to factors

Multivariate Cox proportional hazards regression analyses of mortality complemented by the multiple imputation method including various factors, such as age, sex, cancer stage, presence of procedure(s), presence of radiation, presence of chemotherapy, presence of endocrine therapy, serum albumin level, hemoglobin level, creatinine level, and C-reactive protein level, were performed to examine the significant determinants of death in cancer patients. The presence of DL and the presence of 3 LDH factors in cancer patients were significant negative predictors of mortality (presence of DL: HR = 0.79, $P < .01$; presence of 3 LDH factors: HR = 0.86, $P = .01$; Supplemental Table 1, http://links.lww.com/MD/G494). Cox proportional hazards analysis after adjustment by various models revealed that no statistically significant association between any of the individual cardiovascular conditions and all-cause death, except for the presence of DL and the presence of 3 LDH factors in cancer patients (Fig. 2).

4. Discussions

The main feature of this study is the identification of the relationship between conventional cardiovascular risk factors and mortality in Japanese cancer patients, and the main findings of this study were as follows

1. The prevalence of cardiovascular disease risk factors in cancer patients differed from that in the entire population.
2. The patient background at enrollment differed greatly between the death group and the survival group.
3. Cox proportional hazards analysis after adjustment revealed that although all-cause mortality did not depend on the number of cardiovascular conditions, the presence of DL significantly decreased all-cause mortality.

In cancer treatment, the evaluation and risk stratification of cardiovascular risk factors are the most important tasks in cardio-oncology. Therefore, in the examination of cancer patients, it is important to note any history of cardiovascular disease, the presence or absence of cardiovascular risk factors such as HT, DM, and DL, any history of antineoplastic drug administration, and any history of radiation exposure to the chest in detail.

Because malignant diseases and atherosclerotic diseases share certain risk factors,[17–20] it would be reasonable to expect patients with malignant diseases to have atherosclerotic diseases. Furthermore, malignant diseases[21–23] and atherosclerotic lesions[24–26] are both characterized by inflammation. Therefore, we believe that the pathophysiological links between cancer and cardiovascular disease are solid,[4] and should assume that all cardiovascular diseases contribute to the worsening prognosis of patients with malignant diseases. However, this cohort study revealed that not all coronary risk factors are associated with the prognosis of cancer patients, and the presence of DL is a negative predictor for all-cause mortality.

In the present study, we revealed that DL behaves differently from other cardiovascular conditions. In particular, as the number of factors including DL increases, the mortality rate tends to decrease (Fig. 5). The reason why the number of LDH factors is not a prognostic factor is considered to be that the presence of DL has a great influence as a negative predictor.

With the use of hydroxy-methyl-glutaryl coenzyme A reductase inhibitors (statins) for DL, while the reduction of T-Chol has been achieved and the suppression of coronary artery disease events and the reduction of mortality have been shown in many large clinical trials, there are many reports of increased deaths from nonatherosclerotic diseases due to malignant diseases.[27–29] For example, in the Cholesterol and Recurrent Events (CARE) trial, there was a significant increase in breast cancer in the pravastatin group[30]; moreover, Iwata et al reported an elevated risk of lymphoid malignancy with statin use among Japanese patients.[31] Other increases in prostate cancer[32] and bladder

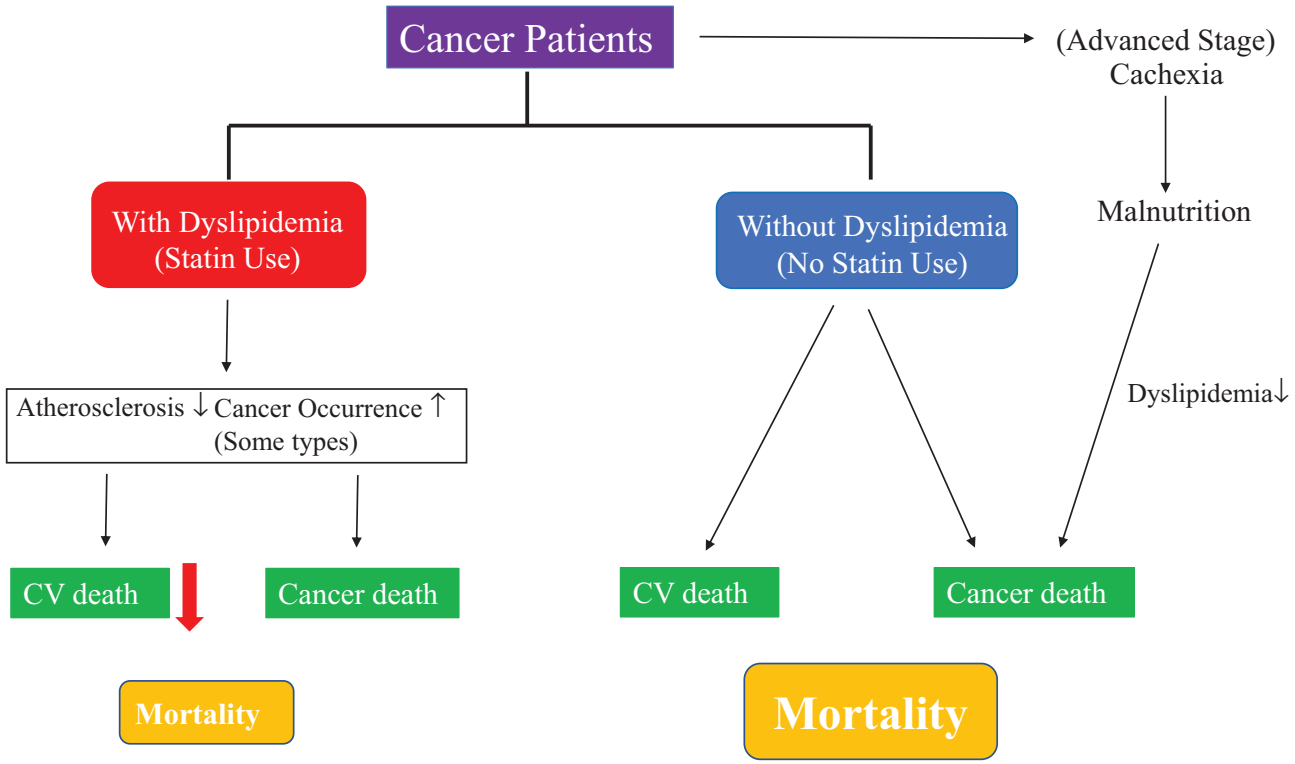

Figure 7. Speculated action of the relationship between the presence of DL and mortality in cancer patients.

cancer[33] have been reported. However, no increase in malignancy was reported in the Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese (MEGA) study, which is an analysis of pravastatin use in the Japanese population.[34]

Previous cohort studies also reported an increased incidence of malignancy in DL patients.[35–37] Furthermore, it has been reported that low HDL cholesterol is involved in the development of breast cancer[38,39] and prostate cancer.[40–42] DL was observed in patients with hematological malignancies[43] and solid cancer[36] and was reported to recover with treatment.[44] In the present study, it was revealed that the presence of DL was negatively associated with all deaths (Fig. 2 and Supplemental Table 1, http://links.lww.com/MD/G494). According to these previous reports, it seems that the relationship between malignant diseases and DL differs depending on the organs at least, and cardiovascular death may have been less due to taking statins. It is unclear whether the presence of DL is the cause or the result of the development of malignant diseases. However, since the results of previous cohort studies differed depending on the organ, subanalysis by organ or tissue type is essential in the present study, as described above. In addition to the effect of statins, since cachexia due to cancer causes malnutrition, advanced cancers with a poorer prognosis are thought to be less likely to develop DL.

Cachexia and cancer malnutrition might make cancer patients with poor prognosis to be less likely to develop DL. Cachectic patients usually but not always lower body mass index, which is associated with an increased risk of tumor progression.[45,46] Elevated lipolysis was reported to be the major reason for fat loss in cancer cachexia.[47–49] Fat loss is associates with shorter survival.[50,51]

Our results were consistent with previous reports in which cardiovascular conditions were determined by ICD.[6,7] Thus, we believe that our results have the incremental value, as we have revealed results based on clinical diagnosis. Although further studies are essential, we revealed the relationship between conventional cardiovascular risk factors and all-cause mortality in cancer patients. Speculated action of the relationship between the presence of DL and mortality in cancer patients was shown in Figure 7.

4.1. Study limitations

This study was a single-center observational study performed in a university hospital that included patients from a large catchment area and thus included a high number and a wide range of cancers among the patients studied, reflecting the broader incidence seen nationally and/or worldwide. Next, the cause of death was unknown. Moreover, it is unknown whether the results obtained accurately reflect the endpoint. The specific factors influencing the association between cancer and cardiovascular risk factors are unclear, in addition to lacking organ/tissue analysis, and the extent to which these factors may contribute to the development of atherosclerosis and the promotion of malignant diseases is unknown. Thus, further pathophysiological and molecular physiological studies, including animal experiments, are warranted. Moreover, we believe that additional large-scale clinical studies may be needed to verify our speculations.

5. Conclusions

Despite the limitations mentioned above, the results of this study demonstrate the relationship between conventional cardiovascu-

lar risk factors and mortality in cancer patients. The presence of DL is a negative risk factor for all-cause mortality in cancer patients.

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