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(分担)研究報告書

がん登録資料を利用した公的情報とのリンケージによる地域相関研究と医療の評価

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研究要旨

１）がん登録、特定検診情報、国勢調査情報から得られるがん情報、生活習慣情報、社会経済的指標などを活用し、地理的に情報をつなぎ最新の情報解析手法を用いたアプローチにより、がん予防対策の策定や評価、がんリスク予測、予防介入の効果予測できる仕組みを構築する。本年度は、生活習慣とがん死亡に関する指標化、視覚化を行った。
２）新規治療の導入が医療にどのように影響を与えたか、住民ベースのがん登録情報を用いて、生存率の経年変化を観察することにより評価した。非小細胞肺癌患者の生存率は1993年から2001年にかけて徐々に改善していった。この改善は、扁平上皮がんよりも腺癌において顕著で、2000年以降に導入された腺癌に対する分子標的薬による可能性が示唆された。

Ａ．研究目的

１）がん登録情報と様々な地理統計とのデータリンケージによる地域相関研究

高齢化社会を迎え 2 人に 1 人ががんに罹る時代、がん罹患リスクを下げる一次予防、がん死亡リスクを下げるための二次予防も重要となってくる。がん登録情報、生活習慣情報、社会経済的情報、医療情報などの保健医療情報を活用し、最新の情報解析手法を用いたアプローチは、がん予防対策の策定や評価、がんリスク予測、予防介入の効果予測に有用である。

本研究は、住民ベースのがん登録情報やその他の保健医療情報などを地理的に連結することによりがん罹患・死亡リスク予測モデルを構築し、生活習慣やがん検診受診率の改善や医療アクセス、シミュレーションによる医療レベルの改善の影響の将来予測、介入の効果予測、がん予防施策の効果的な実施、費用対効果の見直しなどに資する仕組みを構築することを目的とする。

２）新規治療薬が予後に与える影響について（非小細胞肺癌生存率の年次推移）

EGFR 遺伝子変異を示す非小細胞肺癌に対する初の分子標的薬が 2002 年に承認されたが、肺癌診療ガイドラインで分子標的薬の有効性が認められるまで、また、EGFR 遺伝子変異測定が一般病院へ普及するまでに時間を要したため、承認後、本治療の対象は一部に限られていた可能性がある。本研究では、住民ベースのがん罹患情報を用いた生存解析により、分子標的薬治療の普及やその効果を明らかにする。

Ｂ．研究方法

１）がん登録情報と様々な地理統計とのデータリンケージによる地域相関研究

本年度は、下記について実施した。

①公的情報提利用申出と情報の入手について記述する。

②情報の指標化

本年度に情報を入手できた愛知県の人口動態死亡情報を用いて、以下のとおり指標化した。指標化の地理的単位は小学校区とした。公表あるいは情報提供される情報は、小学校区より詳細な町字あるいは町域の情報であるため、町域ポリゴンと、小学校区ポリゴンを用い、面積按分法を用いて小学校区別数を推計した。

がん死亡：愛知県全体の5才階級別がん死亡数と人口を用い、学校区別がん死亡数と5才階級別人口を用いて、小学校区別標準化死亡比を算出した。経験的ベイズ推定により平滑化も行った。

③指標の視覚化

小学校区のShapeファイルを用い、Geographical Information systemを用いて、視覚化を行った。

本研究は、主に愛知県がんセンター重点プロジェクトとして取り組んでいる課題である。

２）新規治療薬が予後に与える影響について（非小細胞肺癌生存率の年次推移）

全国がん罹患モニタリング集計プロジェクトに提供された 7 府県の地域がん登録情報のうち、1993 年から 2011 年に非小細胞肺癌と診断された患者の情報を利用した。診断年により患者を 4 群（期間 1：1993-1997、2：1998-2001、3：2002-2006、4：2007-2011）に分類し、期間別、組織型別の 5 年相対生存率を算出した。次に、過剰ハザードモデルを用いて、性別、

診断時年齢、進展度、組織型を調整し、期間と予後との関連を過剰死亡ハザード比で推定した。

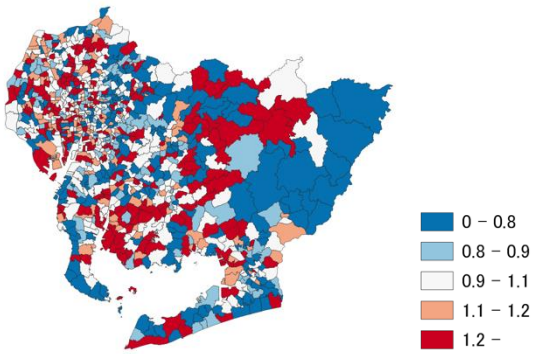
（倫理面への配慮）
いずれの研究のでも、解析のために提供を受けるがん情報やその他の情報は匿名化情報であり、個人を特定できないため、倫理面への配慮は必要ない。しかし、１）については患者の詳細な住所地情報を扱うため、匿名化情報であっても、個人を特定できる可能性も考え、愛知県がんセンター倫理審査委員会の承認を得た上で、情報提供を受けた。

C．研究結果

１）がん登録情報と様々な地理統計とのデータリンケージによる地域相関研究

A.　人口動態調査死亡票ならびに死亡個票情報について

市町村別死因別性別死亡数は、政府統計 E-Stat（https://www.e-stat.go.jp/）より入手した。市町村レベルより詳細な死亡者住所地情報については、人口動態調査の目的外利用申出により、厚生労働省より情報提供を受けた。学校区別の標準化死亡比を算出し、地図上に視覚化した。下図はその一例で、学校区別の男女計胃がんの経験的ベイス推定による標準化死亡比である。（調査票情報の提供を受け、独自に作成・加工した。）



B.　匿名化特定健診情報

特定健診情報は、昨年度 7 月情報提供申出を行い、9 月に審査、10 月に承認され、本年度 4 月に情報提供を受けた。学校区別の標準化罹患比を算出した。視覚化については、匿名特定健診情報についての最小集計単位は 2 次医療圏または市町村と定められているため、視覚化は市町村別に行った。

２）新規治療薬が予後に与える影響について（非小細胞肺癌生存率の年次推移）

解析対象となった非小細胞肺癌患者は 128,247 人であった。各期間の 5 年相対生存率は、期間 1 から 4 の順に、24.2%、29.0%、32.6%、37.7%であった。各組織型の 5 年相対生存率は、扁平上皮癌では 24.1%、23.9%、24.6%、27.2%、腺癌では 25.8%、33.2%、38.5%、45.0%であった。共変量を調整したところ、期間 1 に対する過剰死亡ハザード比は、期間 2 から 4 の順に、0.93（95% 信頼区間：0.91-0.95）、0.78（0.77-0.80）、0.67（0.66-0.69）であった。扁平上皮癌では、期間 1 に対する過剰死亡ハザード比は、それぞれ、1.02（0.98-1.06）、0.92（0.89-0.96）、0.82（0.79-0.85）であり、腺癌では、0.87（0.85-0.90）、0.71（0.69-0.73）、0.59（0.58-0.61）であり、予後に対する期間の効果は両組織で異なっていた（$p = 4.46 \times 10^{-55}$）。

D．考察

１）がん登録情報と様々な地理統計とのデータリンケージによる地域相関研究

本年度入手できた人口動態調査死亡情報と特定健診情報について、指標化、視覚化を行った。昨年度と本年度に情報提供を受けた愛知県がん登録情報、がん死亡情報、生活習慣情報を含む匿名化特定健診情報については、都道府県あるいは厚生労働省に情報利用申出をし、審査を受けた上で提供を受けることができる。提供を受けた情報には詳細な住所情報が含まれるため、個人識別性が高まる可能性が高く、厳格な安全管理措置が要求される。情報提供を受けるにあたっては、組織的、物理的、技術的、人的安全管理措置について十分に準備する必要があると考える。

昨年度は町域レベルで指標化、視覚化を行ったが、本研究成果をがん対策の現場に還元する上で、保健指導単位である小学校区であることを考慮し、本年度は学校区単位の指標化、視覚化を行った。昨年度町域レベルで指標化、視覚化した標準化罹患比や剥奪指標などは、学校区レベルに算出し直して、視覚化を行った。子運後は指標化した情報を用いて、時空間関連解析を実施しする予定である。

２）非小細胞肺癌生存率の推移について

非小細胞肺癌の予後は、最初の分子標的薬の臨床試験が開始された 1998 年-2001 年の期間から向上し始め、承認された 2002 年以降、段階的に改善していた。臨床試験は大学病院やがん専門病院等一部の医療機関でのみ実施されていること、最初の分子標的薬の導入後に重大な副作用が問題となったこと、分子標的薬による治療や EGFR 遺伝子検査が一般病院に普及するまでに時間を要したことから治療が限定的であったことが関係している可能性が示唆される。また、扁平上皮癌と比較して腺癌において生存率の

改善が大きかった。非小細胞肺癌に対する最初の分子標的薬ゲフィニチブは EGFR 遺伝子変異陽性者に著効するが、EGFR 遺伝子変異陽性者には腺癌患者が多いことに起因するものと考えられた。

E. 結論

地域がん登録情報と公的な社会経済的指標や保健医療情報と地理的に連結した研究の進捗を報告した。また、地域がん登録情報を用いて非小細胞肺癌生存率の推移を評価し、新規治療導入による効果について考察した。

F．健康危険情報

（総括研究報告書にまとめて記入）

G．研究発表

１．論文発表

１）Changing trend in mortality rate of multiple myeloma after introduction of novel agents: A population‐based study. Usui Y, Ito H, Koyanagi Y, Shibata A, Matsuda T, Katanoda K, Maeda Y, Matsuo K. Int J Cancer. 2020;147(11): 3102-3109.

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H．知的財産権の出願・登録状況

１．特許取得

なし

２．実用新案登録

なし

３．その他

特記すべきことなし

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添付1

CANCER EPIDEMIOLOGY

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Changing trend in mortality rate of multiple myeloma after introduction of novel agents: A population-based study

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Abstract

Previously, the main treatment for multiple myeloma (MM) was cytotoxic chemotherapies, including autologous stem-cell transplantation (ASCT), but survival benefit in the elderly was limited. More recently, clinical trials and practical experience with novel agents with superior efficacy have shown improved survival, including in the elderly. However, this improvement cannot be simply interpreted as a decline in mortality rate that is an important public health measure of progress against cancer. Here, we assessed the trends in mortality rates of MM in parallel with incidence rates in Japan and the U.S. We used national mortality data and population-based cancer registry data in both countries from 1995 to 2015, during which 74 972 patients in Japan and 229 290 patients in the U.S. died of MM. Trends in mortality and incidence rates were characterized using joinpoint regression analysis. Despite upward trends in incidence, mortality rates showed a significant decrement after 2005 in Japan, with an annual percent change [APC (95% confidence interval)] of −2.5% (−2.9% to −2.1%), and after 2002 in the U.S., with an APC of −2.0% (−2.6% to −1.5%). In both countries, the change in mortality trend coincided with the introduction of the novel agents. Moreover, improvements in mortality were particularly large in patients aged 70 to 79 years, who cannot receive ASCT. Our results indicate that the benefits of novel agents for MM are appreciable at the population level and may encourage further development of novel agents for malignancies that can be widely applied to the patients.

KEYWORDS

incidence rate, Japan, mortality rate, multiple myeloma, SEER

1 | INTRODUCTION

The efficacy and toxicity profiles of novel agents are evaluated by clinical trials in the context of adverse events, response rates and survival time. Although proof of superiority in clinical trials is essential in drug approval, approval itself is not necessarily appreciable as decrease in mortality rates in the general population. Nevertheless, mortality rate in the general population remains an important public health measure of progress against cancer.[1,2] Indeed, prominent interventions sometimes appreciably impact public health as a change in national statistics. Examples include significant improvements in mortality rates reported after interventions with vaccination and with drugs such as aspirin.[3,4] Similarly, we previously reported a dramatic

Abbreviations: AAPC, average annual percent change; APC, annual percent change; ASCT, autologous stem-cell transplantation; ASR, age-standardized rate; CI, confidence interval; ICD, International Classification of Diseases; MCIJ, Monitoring of Cancer Incidence in Japan; MM, multiple myeloma; OS, overall survival; SEER, Surveillance Epidemiology and End Results.

improvement in mortality rates for chronic myeloid leukemia, a hematological neoplasm, after the introduction of imatinib.[5]

Multiple myeloma (MM) is a plasma cell neoplasm which is characterized by clonal plasma cells in the bone marrow, monoclonal protein in the serum and/or urine, and MM-induced organ dysfunction.[6] MM has been generally considered incurable. For many years, the main treatment for MM was cytotoxic chemotherapies. The introduction of high-dose melphalan with autologous stem-cell transplantation (ASCT) in the late 1980s resulted in a significant improvement in overall survival (OS) among transplant-eligible younger patients. In contrast, however, the OS of transplant-ineligible elderly patients did not improve.[7]

Around 2000, the treatment paradigm for MM underwent a remarkable change, thanks to the introduction of novel agents with superior efficacy profiles but different toxicity profiles, such as thalidomide, bortezomib and lenalidomide (Table S1).[8-14] Then, after the introduction of many novel agents, treatment now involves a combination of these novel agents.[15] Improvements in survival have been shown in clinical trials[16,17] and retrospective analyses of hospital-based data,[18,19] including in elderly patients. In fact, a real-world report in the U.S. showed a significant increase in proportion of MM patients treated with novel agents (patients diagnosed in 2000, 8.7%; patients diagnosed in 2014, 61.3%).[20] To date, however, the disease burden of MM in terms of mortality rate at the general population level has not been evaluated.

Here, to quantitatively determine the efficacy of novel agents at the population level, we evaluated the mortality rates of MM in Japan and the U.S. In addition, we also calculated incidence rates of MM in both countries to account for the effect on the mortality during a specified period.

What's new?

Mortality rate is a key public health measure of progress against cancer and is sometimes markedly impacted by the approval of novel anticancer interventions. Here, the authors evaluated mortality and incidence rates of multiple myeloma (MM) in Japan and the United States, searching for trends associated with new therapeutic interventions. Their analyses show that mortality rates of MM decreased significantly after the introduction of novel therapies in the early 2000s, despite increasing trends in MM incidence rates in both countries. Mortality rates improved considerably among older patients, ages 70 to 79, who are unable to undergo autologous stem-cell transplantation.

2 | METHODS

2.1 | Data sources

2.1.1 | Mortality

We used national mortality data in Japan and the U.S. In Japan, the number of deaths from MM was obtained from Vital Statistics Japan (Ministry of Health, Labour and Welfare). In the U.S., publicly available MM mortality data collected by the National Center for Health Statistics were extracted from the National Cancer Institute Surveillance Epidemiology and End Results (SEER) database using SEER*Stat.[21] For both the Japanese and U.S. mortality data, deaths from MM were defined according to SEER Cause of Death Recode [International Classification of Diseases (ICD)-9:203.0, 238.6; ICD-10: C90.0, C90.2].[22] The period specified for mortality analysis was 1995 to 2015, which included the period of introduction of novel agents.

2.1.2 | Incidence

We evaluated the trends in incidence using population-based cancer registry data in Japan and the U.S. Japanese incidence data were obtained from the Monitoring of Cancer Incidence in Japan (MCIJ) project in 2015.[23] Among registries, we selected 13 prefectural cancer registries (Miyagi, Yamagata, Chiba, Kanagawa, Niigata, Fukui, Aichi, Shiga, Osaka, Tottori, Yamaguchi, Nagasaki and Kumamoto) which consistently registered MM to the MCIJ project during the specified period. These databases covered 35.8% of the total Japanese population in 2015. The U.S. incidence data were quoted from the SEER 9 cancer database through SEER*stat,[24] which covered nine high-quality registries (Atlanta, Connecticut, Detroit, Hawaii, Iowa, New Mexico, San Francisco-Oakland, Seattle-Puget Sound and Utah) that accounted for 9.4% of the total U.S. population in 2015. Patients with MM in Japan and the U.S. were defined as those registered with 9731/3, 9732/3 and 9734/3 (ICD-O-3), which corresponded to 203.0 (ICD-9), 238.6 (ICD-9), C90.0 (ICD-10) and C90.2 (ICD-10). The period specified for incidence analysis was 1995 to 2015, namely, the same as the period of mortality analysis.

2.1.3 | Population

Population data were used to calculate mortality and incidence rates of MM. In Japan, total population data were obtained from the Cancer Information Service of the National Cancer Center, Japan.[25] In the U.S., total population data were extracted from the SEER database using SEER*Stat.[26]

2.1.4 | Statistical analysis

We calculated annual age-standardized rates (ASRs; standardized by the world standard population[27]) for mortality and incidence of MM. We analyzed the trends in mortality and incidence rate, and calculated annual percent changes (APCs) and average annual percent changes (AAPCs)[28] using a joinpoint regression model. This model has been described in detail elsewhere.[29,30] Briefly, joinpoint regression analysis is a statistical method that analyzes changing trends over consecutive

TABLE 1 Subject characteristics

	Japan		U.S.	
	Incidence (n = 33 688)[a]	Mortality (n = 74 972)	Incidence (n = 37 121)[b]	Mortality (n = 229 290)
Age (%)				
0-49	1191 (3.54)	1232 (1.64)	2829 (7.62)	7541 (3.29)
50-59	3426 (10.17)	5151 (6.87)	6138 (16.54)	23 703 (10.34)
60-69	8207 (24.36)	15 211 (20.29)	9389 (25.29)	49 366 (21.53)
70-79	11 667 (34.63)	26 459 (35.29)	10 686 (28.79)	75 325 (32.85)
80+	9197 (27.30)	26 919 (35.91)	8079 (21.76)	73 355 (31.99)
Sex (%)				
Male	17 256 (51.22)	37 643 (50.21)	20 395 (54.94)	120 753 (52.66)
Female	16 432 (48.78)	37 329 (49.79)	16 726 (45.06)	108 537 (47.34)

[a]Incidence data in Japan were obtained from 13 registries (Miyagi, Yamagata, Chiba, Kanagawa, Niigata, Fukui, Aichi, Shiga, Osaka, Tottori, Yamaguchi, Nagasaki and Kumamoto).
[b]Incidence data in the U.S. were obtained from nine registries (Atlanta, Connecticut, Detroit, Hawaii, Iowa, New Mexico, San Francisco-Oakland, Seattle-Puget Sound and Utah).

TABLE 2 Trends in age-specific mortality and incidence rate

		Trend 1		Trend 2		Trend 3	
	AAPC (95%CI)	Period	APC (95%CI)	Period	APC (95%CI)	Period	APC (95%CI)
Japan							
Total							
Mortality	**−1.5 (−1.7 to −1.2)**	1995-2005	−0.4 (−0.8 to 0.0)	2005-2015	**−2.5 (−2.9 to −2.1)**		
Incidence	**0.9 (0.6 to 1.2)**	1995-2015	**0.9 (0.6 to 1.2)**				
Male							
Mortality	**−1.5 (−1.9 to −1.1)**	1995-2004	−0.4 (−1.2 to 0.3)	2004-2015	**−2.3 (−2.8 to −1.8)**		
Incidence	**0.8 (0.5 to 1.1)**	1995-2015	**0.8 (0.5 to 1.1)**				
Female							
Mortality	**−1.5 (−1.9 to −1.1)**	1995-2005	−0.2 (−0.9 to 0.4)	2005-2015	**−2.7 (−3.4 to −2.1)**		
Incidence	**0.9 (0.4 to 1.3)**	1995-2015	**0.9 (0.4 to 1.3)**				
U.S.							
Total							
Mortality	**−1.1 (−1.4 to −0.9)**	1995-2002	**−0.9 (−1.4 to −0.5)**	2002-2009	**−2.0 (−2.6 to −1.5)**	2009-2015	−0.3 (−0.8 to 0.3)
Incidence	0.9 (−0.3 to 2.0)	1995-2007	0.4 (−0.1 to 0.9)	2007-2010	3.9 (−3.6 to 12.0)	2010-2015	0.1 (−1.4 to 1.6)
Male							
Mortality	**−1.2 (−1.3 to −1.1)**	1995-2015	**−1.2 (−1.3 to −1.1)**				
Incidence	**1.1 (0.9 to 1.4)**	1995-2015	**1.1 (0.9 to 1.4)**				
Female							
Mortality	**−1.4 (−1.8 to −0.9)**	1995-2002	**−1.0 (−1.7 to −0.3)**	2002-2008	**−2.9 (−4.0 to −1.7)**	2008-2015	−0.4 (−1.1 to 0.3)
Incidence	**0.9 (0.5 to 1.2)**	1995-2015	**0.9 (0.5 to 1.2)**				

Note: Values significantly different from zero (two-sided $P < .05$, calculated using a *t*-test) are highlighted in bold. Japan: Phase I/II study of the first novel agent was started in May 2004, and approval of the first novel agent was received in October 2006. U.S.: Phase I/II study of the first novel agent was started in December 1997, and approval of the first novel agent was received in May 2003.
Abbreviations: APC, annual percent change; AAPC, average annual percent change; CI, confidence interval.

segments of time and evaluates the significance of increase or decrease within each segment after identifying the best fitting model. Within each segment, the log of the rate is modeled as a linear function, yielding the annual exponential rate of change. For analysis, uncorrelated error models were used. The minimum number of joinpoints in the model was set as zero and the maximum number as three. The SE was estimated for each year. Two-sided *P*-values < .05 were considered statistically significant. In describing the trends, we defined an increase or decrease as occurring when the APC or AAPC of the trends was statistically significant; otherwise, we defined the

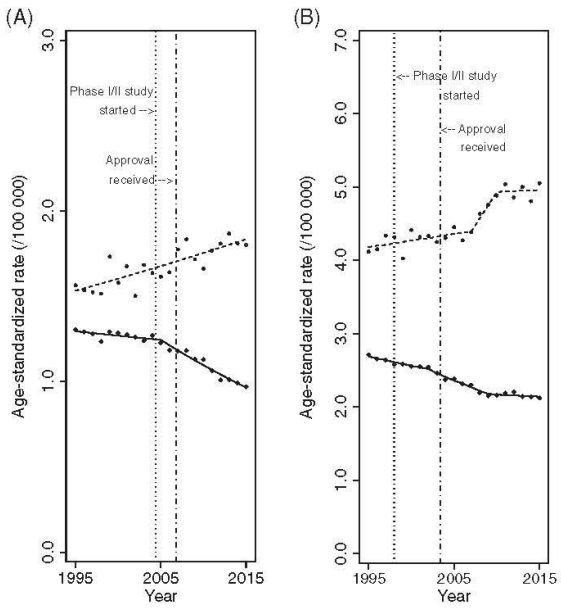

FIGURE 1 Overall trends in age-standardized mortality and incidence rate of multiple myeloma. Overall trends in age-standardized mortality and incidence rate of multiple myeloma in, A, Japan and B, the U.S. World standard population was applied. White circles indicate the observed incidence rate, *black diamonds indicate the observed mortality rate, and lines indicate modeled rates estimated by joinpoint regression analysis. Vertical lines at left show the first Phase I/II study of a novel agent and those at right show the first approval of a novel agent*

trend as stable. We also performed stratified analysis by age category, classified as age 0 to 49, 50 to 59, 60 to 69, 70 to 79 and 80 years or older. All analyses were conducted using Stata, version 15.1 software (Stata Corp., College Station, Texas) and Joinpoint Regression Program, version 4.6.0.0 (U.S. National Cancer Institute, Bethesda, Maryland).

3 | RESULTS

Subject characteristics are shown in Table 1. A total of 74 972 patients in Japan and 229 290 in the U.S. died of MM during the period. The proportion of males was higher in both incidence and mortality in both countries, and more than half of the patients were aged 70 years or older at diagnosis in both countries (61.9% in Japan and 50.6% in the U.S.).

Trends for ASRs in mortality and incidence analyzed by joinpoint regression analysis are shown in Table 2 and summarized in Figure 1, and trends for ASRs sorted by sex are summarized in Figure S1. In Japan, while the incidence rate showed a significant increasing trend [APC 0.9%, 95% confidence interval (CI); 0.6% to 1.2%], the mortality rate significantly turned to decrease in 2005, with an APC of −2.5% (95% CI; −2.9% to −2.1%; Table 2) (joinpoints and their 95% CIs are shown in Table S2). Similarly, while the incidence rate showed an upward trend (APC 0.9% and its 95% CI; −0.3 to 2.0%), the magnitude of the downward trend in mortality rate became larger in 2002 with an APC of −2.0% (95% CI; −2.6% to −1.5%) in the U.S (Table 2) (joinpoints and their 95% CIs are shown in Table S2). As shown in Figure 1, the change in mortality trends in both countries appeared to coincide with the timing of introduction of the novel agents.

TABLE 3 Trends in age-categorized mortality and incidence rate

		Trend 1		Trend 2		Trend 3	
	AAPC (95% CI)	Period	APC (95% CI)	Period	APC (95% CI)	Period	APC (95% CI)
Japan							
0-49							
Mortality	−1.3 (−4.0 to 1.6)	1995-1997	11.6 (−13.1 to 43.4)	1997-2007	**−5.8 (−8.2 to −3.4)**	2007-2015	1.6 (−2.0 to 5.3)
Incidence	**2.5 (1.5 to 3.5)**	1995-2015	**2.5 (1.5 to 3.5)**				
50-59							
Mortality	**−2.6 (−3.5 to −1.6)**	1995-2008	**−1.0 (−1.9 to −0.2)**	2008-2015	**−5.3 (−7.8 to −2.8)**		
Incidence	**1.7 (1.1 to 2.2)**	1995-2015	**1.7 (1.1 to 2.2)**				
60-69							
Mortality	**−2.3 (−2.6 to −2.0)**	1995-2015	**−2.3 (−2.6 to −2.0)**				
Incidence	**0.8 (0.3 to 1.3)**	1995-2015	**0.8 (0.3 to 1.3)**				
70-79							
Mortality	**−1.2 (−1.6 to −0.8)**	1995-2004	**1.2 (0.4 to 2.0)**	2004-2015	**−3.1 (−3.7 to −2.6)**		
Incidence	**0.7 (0.3 to 1.1)**	1995-2015	**0.7 (0.3 to 1.1)**				
80+							
Mortality	0.0 (−0.2 to −0.3)	1995-2015	0.0 (−0.2 to −0.3)				
Incidence	**0.6 (0.2 to 1.0)**	1995-2015	**0.6 (0.2 to 1.0)**				

(Continues)

TABLE 3 (Continued)

		Trend 1		Trend 2		Trend 3	
	AAPC (95% CI)	Period	APC (95% CI)	Period	APC (95% CI)	Period	APC (95% CI)
U.S.							
0-49							
Mortality	**−2.3 (−2.8 to −1.8)**	1995-2015	**−2.3 (−2.8 to −1.8)**				
Incidence	**2.3 (1.7 to 2.9)**	1995-2015	**2.3 (1.7 to 2.9)**				
50-59							
Mortality	**−2.3 (−2.5 to −2.1)**	1995-2015	**−2.3 (−2.5 to −2.1)**				
Incidence	1.0 (0.0 to 2.1)	1995-2007	−0.3 (−1.6 to 1.0)	2007-2015	**3.0 (1.0 to 5.1)**		
60-69							
Mortality	**−2.3 (−2.5 to −2.0)**	1995-2015	**−2.3 (−2.5 to −2.0)**				
Incidence	**0.7 (0.3 to 1.0)**	1995-2015	**0.7 (0.3 to 1.0)**				
70-79							
Mortality	**−0.8 (−1.3 to −0.4)**	1995-2002	0.1 (−0.5 to 0.8)	2002-2008	**−2.1 (−3.1 to −1.0)**	2008-2015	**−0.7 (−1.4 to 0.0)**
Incidence	**1.0 (0.7 to 1.4)**	1995-2015	**1.0 (0.7 to 1.4)**				
80+							
Mortality	0.5 (0.0 to 0.9)	1995-2002	0.5 (−0.3 to 1.3)	2002-2008	−0.9 (−2.2 to 0.3)	2008-2015	**1.6 (0.9 to 2.3)**
Incidence	**0.7 (0.2 to 1.2)**	1995-2015	**0.7 (0.2 to 1.2)**				

Note: Values significantly different from zero (two-sided $P < .05$, calculated using a t test) are highlighted in bold. Japan: Phase I/II study of the first novel agent was started in May 2004, and approval of the first novel agent was received in October 2006. U.S.: Phase I/II study of the first novel agent was started in December 1997, and approval of the first novel agent was received in May 2003.
Abbreviations: APC, annual percent change; AAPC, average annual percent change; CI, confidence interval.

The trends for age-specific rates in mortality and incidence are shown in Table 3 and Figure 2. In both countries, mortality rates had a trend of decline in patients aged less than or equal to 79 years in both countries with upward trends in incidence rates after the introduction of novel agents. Especially, mortality rate of patients aged 70 to 79 years showed remarkable trends in both countries. In Japan, mortality rate changed to decrease in 2004 with an APC of −3.1% (95% CI; −3.7% to −2.6%), after an upward trend in mortality rate (APC 1.2%, 95% CI; 0.4% to 2.0%; Table 3). The magnitude of decline of mortality rate was remarkable in this age-category with higher mortality rate itself than the other age categories less than or equal to 69 years of age, although the APC was not larger than the others (Figure 2). In the U.S., mortality rate changed to decrease in 2002 with an APC of −2.1% (95% CI; −3.1% to −1.0%), after a stable trend in mortality rate (APC 0.1%, 95% CI; −0.5% to 0.8%; Table 3). On the contrary, mortality rates did not decline in patients aged 80 years or older in both countries despite the same trends in incidence as in other age categories.

4 | DISCUSSION

In our study, we showed that the mortality rates of MM changed to a downward trend in 2005 in Japan and in 2002 in the U.S. After these changes in mortality trends, the ASRs declined with an APC of approximately 2.0% in the two countries. These changes in mortality trends appeared to coincide with the introduction of novel agents in both countries. MM was previously a lethal condition, allowing the possibility that mortality rates would decline immediately after their introduction. Given that the incidence rates did not decline over the observation period, and indeed increased, it would be reasonable to consider that the incorporation of novel agents into the treatment of MM had the effect of improving the mortality rate of MM in the general population. To the best of our knowledge, this is the first population-based study to evaluate the mortality and incidence rates of MM in the era of novel agents in Japan and the U.S.

Patient age is an important factor in clinical decision making for treatment indications of MM.[31] One interesting characteristic of our study is its evaluation of trends in mortality rate by age category, which showed heterogeneity. For example, the age-specific mortality rates showed a prominent decrement among patients aged 70 to 79 years after the emergence of novel agents (Figure 2). Rates declined in both countries, after an initial increasing trend in Japan and after a stable trend in the U.S. Patients aged 70 to 79 years are transplant-ineligible and have not benefited from ASCT.[7] In contrast, novel agents are recommended as an initial therapy option even for elder transplantation-ineligible patients, and these patients got a wider availability of treatment after introduction of novel agents.[15,32] Our finding suggests that the benefits of novel agents may be particularly large in patients who received less benefit from conventional chemotherapies, such as ASCT. This benefit in turn represents a reduction in disease burden in terms of mortality at the general population level. Indeed, many clinical studies exclude elderly patients, necessarily resulting in the failure to fully evaluate the subject disease

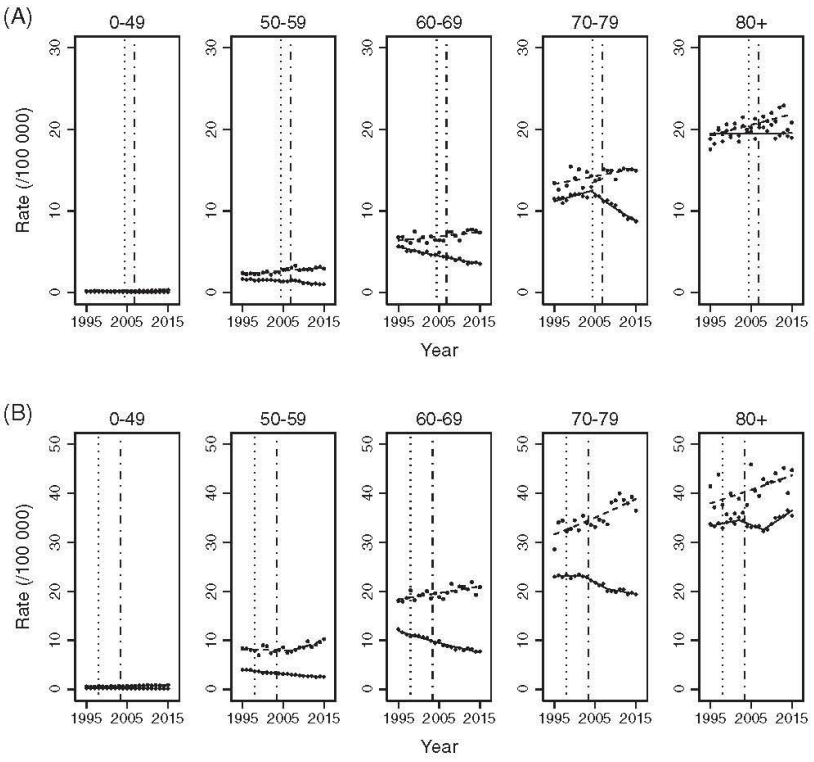

FIGURE 2 Age-specific trends in mortality and incidence rate of multiple myeloma. Age-specific mortality and incidence rate of multiple myeloma in, A, Japan and B, the U.S. White circles indicate the observed incidence rate, black diamonds indicate the observed mortality rate, and lines indicate modeled rates estimated by joinpoint regression analysis. Vertical lines at left show the first Phase I/II study of a novel agent and those at right show the first approval of a novel agent

population. Population-based study is particularly effective and necessary in such less studied populations.

The age-specific mortality rates in patients aged less than or equal to 69 years also showed declining trends in the era of novel agents in both countries. However, we did not observe any joinpoints in several age groups after introduction in either country, namely in those aged 0 to 49, 50 to 59 or 60 to 69 years. The mortality rates in patients aged less than or equal to 69 years were declining before the introduction of novel agents, possibly because patients aged less than or equal to 69 years were transplant-eligible. The additional treatment options afforded by the introduction of novel agents might also explain the continuous decline among these age populations in both countries, in part at least.

Of note, the age-specific mortality rates in patients aged 80 years or older did not show any decline in either country, although the magnitude of change in incidence was not as large as in other age categories (Figure 2 and Table 3). This may be because elderly patients generally have many comorbidities and may be less tolerant to even novel agents.[33] The novel agents are known to improve MM-related complications, such as kidney impairment,[34] and may also confer benefits additional to the decline in mortality rate. In patients aged 80 years or older, it is desirable to evaluate the benefits of novel agents from aspects other than mortality rate.

A number of previous population-based studies have reported improvements in the survival time of MM in the era of these novel agents. In Japan, the 5-year relative survival rate from 2003 to 2008 was reported to have improved (1997-1999, 29.8%; 2000-2002, 29.0%; 2003-2005, 32.6%; 2006-2008, 36.4%).[25,35] In the U.S., the 5-year relative survival rate improved significantly from 2002 to 2007 (1993-1995; 31.7%, 1996-2001; 34.6%, 2002-2004; 42.5%, 2005-2007; 46.4%, respectively).[36] In general, survival is undoubtedly an important parameter of disease prognosis, and can be influenced by earlier diagnosis without postponing the time of death (lead-time bias) and increased detection of indolent cancers (length bias), and so on.[1,2] Given this, improvement of survival estimates can be overestimated regardless of the actual clinical impact of treatment. We overcame this potential bias in survival evaluation in a clinical study setting by applying population-based mortality rates and showing a decline in mortality rates of MM in the era of novel agents.

Our study has several strengths. First, to the best of our knowledge, it is the first to evaluate mortality and incidence rates in patients with MM, which are essential to the setting of public health priorities. Second, we used unbiased population-based data, which namely included all MM patients irrespective of whether or not they were treated with novel agents. If any misclassification were present, it would likely be nondifferential and therefore likely to underestimate the significance. Nevertheless, mortality rates have declined significantly in the era of novel agents. Our findings show the remarkable impact of these novel agents on patients with MM.

Several limitations also should be noted. First, we observed the coincidence in timing of the introduction of novel agents and the decline in mortality rates. In other words, we did not directly evaluate

the impact of novel agents on mortality rates. Accordingly, other factors might have biased the interpretation of our results, such as changes in supportive therapies for MM or changes in incidence trends. MM is accompanied by a range of complications such as renal failure, infection, anemia, bone-related complications and others, all of which increase the risk of mortality. For example, bone-modifying agents reduce the risk of bone-related events in MM patients.[37] Therefore, new supportive therapies including bone-modifying agents for these conditions might also have contributed to decreasing mortality rates throughout the period. In addition, trends in incidence rates might also affect trends in mortality rates. Because the quality of registration has improved and the number of registrations has increased since 2005 in Japan,[23] the observed increasing trends in incidence in our study might simply be an artificial increase from increased registration. This possibility is unlikely, however, because we observed the same upward trend in incidence [ASR; APC 0.8% (95% CI; 0.4% to 1.2%), data not shown] using data from four Japanese registries with high and stable registration quality. In addition, similar increasing trends in incidence were observed in different populations in the U.S. with high-quality registration. Based on these findings, we believe that the observed upward trends of incidence were not biased by improving registration quality.

Second, our data did not include clinical information for individuals, such as clinical stage, cytogenetic abnormality and complications. Therefore, our analyses did not indicate differences in improvement of mortality rates by clinical subtype. Nevertheless, our data show a remarkable declining trend in the mortality rates of MM in patients from various real-world clinical backgrounds after the introduction of these novel agents. In addition, novel agents are widely recommended for a very broad range of patients, such as transplantation-eligible patients, transplantation-ineligible patients, patients with newly diagnosed disease, and patients with relapse/refractory disease.[15] In fact, the real-world report showed that the number of MM patients using novel agents has significantly increased.[20] Besides, a previous study reported that the improvement of survival in the era of novel agents was remarkable in the patients over 65 years old.[18]

In conclusion, we found that the disease burden of MM in terms of mortality rate significantly reduced in both countries after introduction of novel agents despite increasing trends in incidence rate. Our results indicate that the introduction of novel agents for MM has had a remarkable impact on the general population level. In addition, those who received greater benefit from these novel agents tended to be patients aged 70 to 79 years, who had received less benefit from conventional chemotherapy, such as ASCT. Our results may encourage further development of more effective and less toxic novel agents for malignancies, including MM that can be administered to patients across a wide range, including elderly patients, although evaluation the data for health system in terms of economic sustainability is required.

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CONFLICT OF INTEREST

Y. U. was awarded the "Fujimoto Isaburo Prize", founded by the Japanese Association of Cancer Registries. K. K. received a JMWH Bayer Grant. The remaining authors declare no potential competing interests.

DATA ACCESSIBILITY

The data that support the findings of our study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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