厚生労働科学研究費補助金（がん対策推進総合研究事業）
（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

研究分担者　伊藤秀美　愛知県がんｾﾝﾀｰ研究所　がん情報・対策研究分野　分野長

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、愛知県のがん罹患、死亡の社会経済格差の大きさが都市度によって違うことを示した。2）匿名化されたがん登録情報を用いて、頭頚部がんの詳細部位別の罹患の動向を Joinpoint 解析で評価した。

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）頭頚部がんの詳細部位別罹患の動向：1993-2015 年の地域がん登録データの利用（MCIJ 詳細集計）

喫煙と飲酒は頭頚部がんの重要なリスク要因である。また、欧米を始めとする先進国では、ヒトパピローマウイルス（HPV）感染による中咽頭がんの増加が注目されている。しかし、日本における詳細部位別の罹患の推移を評価した研究はほとんどない。そこで本年度、日本の地域がん登録情報を用いて、日本における頭頚部がんの罹患動向を検討した。

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 匿名化全国がん登録情報の入手について記述する。

② 肺がんの罹患、死亡と地理的剥奪指標との関連の評価

2013-2017年のがん罹患情報（個別）を愛知県から、2013-2017年のがん死亡情報（集計値）を政府統計の総合窓口（e-Stat）からダウンロードし、小学校区別の標準化罹患比・死亡比（Standardised Incidence and Mortality Ratio : SIR/SMR）ならびにそれらの経験ベイズ推計値(Emprical Bayes(EB)EIR/SMR)を算出し地図上に視覚化した。また、2015年の国勢調査情報をe-Statからダウンロードし、小学校区別の地理的剥奪指標（Areal Deprivation Index; ADI）を算出し、EBSIR/EBSMRとADIとの関連を線型回帰モデル（分散加重最小二乗法）にて評価した。これらの関連の都市度によるheterogeneietyも評価した。SIRとSMRの集積性をFlex Scan法で評価し、クラスターを地図上に視覚化した。クラスター内外におけるADIの分布の箱ひげ図を作成した。これらの解析はすべて名古屋、市部、群部に分けて行った。

２） 頭頚部がんの詳細部位別罹患の動向：1993-2015年の地域がん登録データの利用（MCIJ詳細集計）

MCIJ詳細集計データのうち精度の良い9県の情報を用いて、1993-2015年の年齢調整罹患率（世界人口）を詳細部位別（口唇、口腔、唾液腺、鼻咽頭、中咽頭、下咽頭、喉頭、鼻及び副鼻腔、中耳）に算出した。さらに、Joinpoint解析により、これらの年齢調整罹患率の推移における変曲点と、隣り合う変曲点間の年変化率を算出した。

（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

① 詳細な患者住所情報を含む全国がん登録情報の入手について

これまで本研究は愛知県を対象に実施してきたが、他の県の情報を活用して研究を展開するため、複数県の全国がん登録情報提供の申出を行った。以下、その経過を示す。

前年度 3 月に事前相談を開始し、4 月に申出書を提出した。地理疫学研究を実施するために、患者の診断時住所情報（J-LIS の 11 桁コード　町字レベルまでのテキスト情報）の提供も希望したが、事前相談の段階で詳細な診断時患者住所情報の提供は、本研究は地域レベルで他の情報と連結することで個人識別性を高める可能性があるため、認められなかった。診断時患者住所都道府県コードは基本提供項目に含まれる。患者診断時住所地理的属性選択提供項目として、保健所コード、医療圏コード、市町村コードまでは研究の目的に合致していれば、提供を受けることができる。しかし、市町村レベ

ルより詳細な小学校区、町域、町字レベルの患者住所情報提供は個人情報保護の観点から研究の目的や意義に合致していたとしても難しかった。詳細住所情報の粒度を小学校区とし、基本提供項目のうち 1 歳刻みの年齢を 5 歳きざみに、局在部位は ICD-10 や ICD-O-3 の 4 桁コードでなく、男女の主要 5 部位を網羅する部位（胃、大腸、肺、肝、前立腺、乳房、子宮、膵）のみが判別できる項目に丸めて提供を受け、診断年は提供を受けないといった個人識別性を下げる工夫を提案した。しかし、匿名化された情報の提供を審議する国立がん研究センターの審議会では、審議するかどうかの判断がつかず、7 月に親会議である厚生労働審議会がん登録部会で、まずは審議する場として匿名化情報提供の審議会が妥当かどうか検討された。結果、10 月末に匿名化された情報として審議され、条件付き承認となった。事前相談開始から承認まで 8 ヶ月、令和 4 年 3 月 31 日現在でいまだ詳細住所情報の提供は受けていない。なお、公表については、統計解析に小学校区別の指標を用いることは可能だが、地図上での視覚化、関連解析の散布図等、小学校区の特定につながる可能性のある公表は認められなかった。

② 肺がんの罹患、死亡と地理的剥奪指標との関連の評価

愛知県の小学校別 ADI を地図上に視覚化しした（図 1）小学校区別の肺がんの EBSIR と EBSMR の分布を地図上に視覚化した。また、SIR、SMR の集積性を地図上に視覚化し（図 2　死亡のみ）、クラスター内外の ADI に分布の都市度別の箱ひげ図（図 3　死亡のみ）において、がん罹患・死亡と地理的剥奪指標との関連をみたところ、都市化の進む名古屋市において肺がん死亡が集積しない地域に比べて集積する地域では ADI が高かったが、市部、群部においてはその差がなかった。

２）　頭頚部がんの詳細部位別罹患の動向：1993-2015年の地域がん登録データの利用（MCIJ詳細集計）

男女とも、口腔がん、唾液腺がん、中咽頭がんは増加傾向を示した（口腔：年間変化率（APC）男性1.2%、女性1.9%、唾液腺：APC 男性2.2%、女性1.9%）。唾液腺：男性2.2%、女性3.1%、口腔咽頭。中咽頭：男性5.0%、女性7.6%）。また、下咽頭がんは男性で増加傾向（APC4.1%）、上咽頭がんと喉頭がんは男性で減少傾向（上咽頭：APC-2.7%、喉頭：-1.1%）であった。

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

①　詳細な患者住所情報を含む全国がん登録情報の入手について

詳細診断時患者住所情報を含む全国がん登録情報の提供について、個人情報保護の観点から、極めて慎重に審議しされた。本研究に対して情報提供申出は承認されたが、先例類型となるものではなかった。個人識別性を高める可能性のある情報の提供において、研究の意義と個人情報保護の観点とのバランスが非常に重要であった。

分担研究者は、生活習慣の地理的指標の算出のため匿名化NDB情報の一部である特定健診情報の提供も受けている。特定健診

情報には特定健診受診者の住所の郵便番号情報（町域レベル）が含まれており、この情報は他のコードに加工した上での提供が認められている。さらに市町村レベルより詳細な郵便番号レベルでの地図上への視覚化を認めていないが統計解析に含めることは可能という点では全国がん登録情報の利用に関する条件と同じであったが、NDB情報においては散布図の作成を認めているのに対し、全国がん登録情報の利用においては認められなかった。例えば、小学校区のADIとEBSIRの関連を見るためのプロットでは、ADIとEBSIRの算出値から小学校区を特定できる可能性が否めないためと思われた。NDB情報利用においては、個人識別性を高める可能性のある情報は提供するが公表時点で制御する、全国がん登録情報の利用においては、情報提供時においても制御し、さらに公表時点にさらに厳格な条件を課すという方針のようである。

② 肺がんの罹患、死亡と地理的剥奪指標との関連の評価

がん罹患や死亡の地理的な社会経済的格差は都会度が高くなるほど大きかった。これは、都会度が高いほど、社会経済的要因とがん罹患・死亡との間に介在するリスク要因となる喫煙等の生活習慣、検診受診、保健医療サービスへのアクセス、その他物理的環境、社会サービス、人間関係や社会、心理的ストレスの社会経済格差が大きいことに起因する可能性が示唆される。地理的な社会経済格差自体に介入することは困難である中、変容可能な媒介因子の格差縮小に向けた対策が、がんの罹患や死亡の格差につながるであろう。

２） 頭頚部がんの詳細部位別罹患の動向：1993-2015年の地域がん登録データの利用（MCIJ詳細集計）

本研究では、頭頚部がんの詳細部位別年齢調整罹患率の推移を、1993-2015年の日本の住民ベースのがん登録情報を用いて評価した日本初の研究である。。頭頚部がん全体では観察期間中、男性、女性ともに増加傾向を示した。部位別では、男性では口腔がん、唾液腺がん、女性では口腔、唾液腺、中咽頭がんで増加傾向が認められた。また、男性では上咽頭および喉頭がんは減少傾向にあった。本研究で増加傾向を示した亜部位に対する予防戦略の構築が重要と考えられた。

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頭頚部がんの詳細部位別の罹患の推移を評価した。

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

Trends in the incidence of head and neck cancer by subsite between 1993 and 2015 in Japan. Kawakita D, Oze I, Iwasaki S, Matsuda T, Matsuo K, Ito H. Cancer Med. 2022 Mar;11(6):1553-1560.

２．学会発表

住民ベースのがん罹患情報を用いた非小細胞肺がん患者の予後における分子標的薬による影響の評価. 谷山祐香里、尾瀬功、小栁友理子、伊藤ゆり、松田智大、松尾恵太郎、伊藤秀美. （口演、第 32 回日本疫学会学術集会、2021.1.26−28、千葉（オンライン））

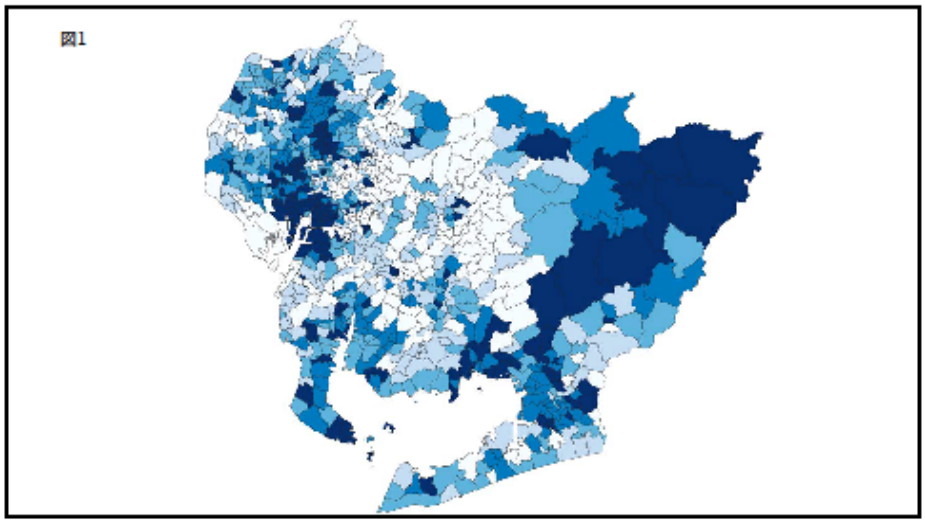
H．知的財産権の出願・登録状況

１．特許取得

なし

２．実用新案登録

なし



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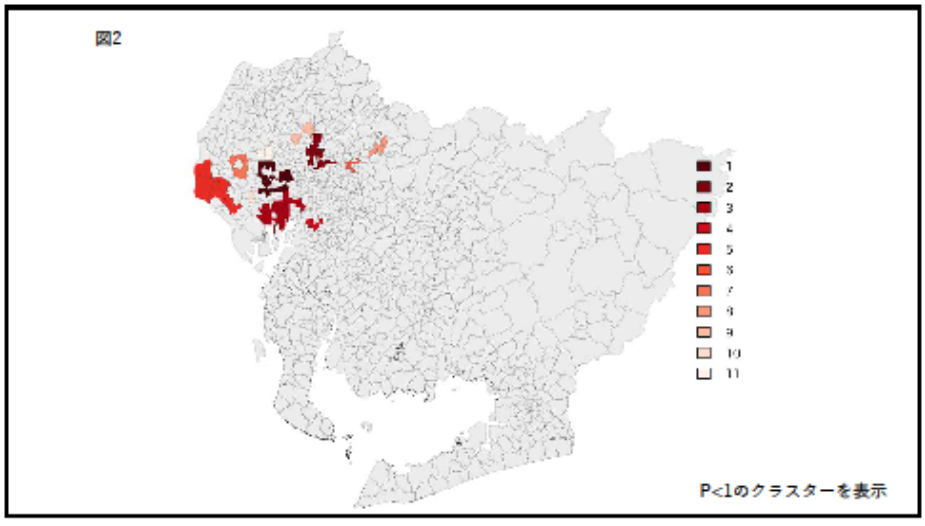

2

1

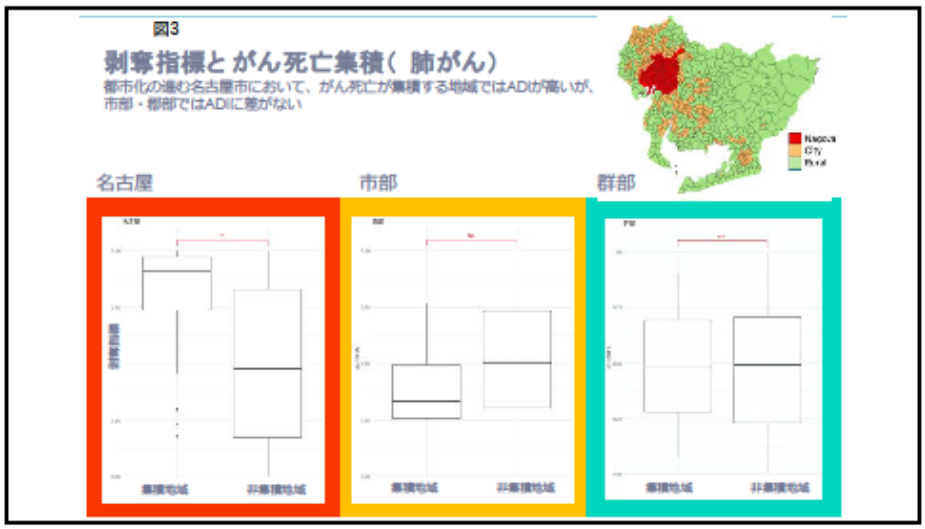
図3
剥奪指標と がん死亡集積（ 肺がん）
都市化の進む名古屋市において、がん死亡が集積する地域ではADが高いが、
市部・郡部ではADに差がない
名古屋
市部
群部
集積地域
非集積地域

3

2

Journal of Epidemiology

Original Article J Epidemiol 2019;29(9):347-353

Trends in Small-Cell Lung Cancer Survival in 1993–2006 Based on Population-Based Cancer Registry Data in Japan

Isao Oze[1], Hidemi Ito[2,3], Yoshikazu Nishino[4], Masakazu Hattori[5], Tomio Nakayama[6], Isao Miyashiro[7], Keitaro Matsuo[1,3], and Yuri Ito[8]

[1]Division of Cancer Epidemiology and Prevention, Department of Preventive Medicine, Aichi Cancer Center Research Institute, Nagoya, Japan
[2]Division of Cancer Information and Control, Department of Preventive Medicine, Aichi Cancer Center Research Institute, Nagoya, Japan
[3]Department of Epidemiology, Nagoya University Graduate School of Medicine, Nagoya, Japan
[4]Department of Epidemiology and Public Health, Kanazawa Medical University, Ishikawa, Japan
[5]Department of Cancer Therapy Center, Fukui Prefectural Hospital, Fukui, Japan
[6]Division of Screening Assessment and Management, Screening Research Group, Center for Public Health Sciences, National Cancer Center, Tokyo, Japan
[7]Cancer Control Center, Osaka International Cancer Institute, Osaka, Japan
[8]Department of Medical Statistics, Research & Development Center, Osaka Medical College, Takatsuki, Osaka, Japan

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ABSTRACT

Background: Lung cancers are classified into small-cell lung cancer (SCLC) and non-small-cell lung cancer due to their different treatment and prognosis. Although many studies have reported the specific survival of SCLC patients treated at cancer hospitals, survival from population-based data has rarely been reported.

Methods: We analyzed survival of SCLC cases diagnosed from 1993 through 2006 from a population-based cancer registry of six prefectures. To assess trends in SCLC survival, we defined three periods that mirrored developments in SCLC treatment: period 1, 1993–1998; period 2, 1999–2001; and period 3, 2002–2006. Assessments were based on relative survival (RS), excess hazard, and conditional survival.

Results: A total of 10,911 SCLC patients were analyzed. Five-year RS among limited disease SCLC (LD-SCLC) in periods 1 to 3 was 16.8%, 21.1%, and 21.4%, respectively. Five-year RS among extensive disease SCLC (ED-SCLC) in periods 1 to 3 was 2.3%, 2.8%, and 2.7%, respectively. Improvement in 5-year RS in periods 2 and 3 compared with period 1 was significant among both LD- and ED-SCLC patients (all $P < 0.001$). Conditional 5-year RS of LD-SCLC increased from 21% at year 0 to 73% at year 5, while that of ED-SCLC was 3% at year 0 and 53% at year 5.

Conclusions: The prognosis of SCLC patients improved from 1999–2001 but plateaued in 2002–2006, after which no further significant improvement was seen. Continuous survey based on population-based data is helpful in monitoring the impact of developments in treatment.

Key words: cancer registry; population-based; small cell lung cancer; survival

INTRODUCTION

Lung cancers are classified into two broad classes, small-cell lung cancer (SCLC) and non-small-cell lung cancer (NSCLC).[1,2] These cancers differ biologically and, accordingly, also differ in their therapy and prognosis.[3] National rates of survival of total lung cancer patients have been reported for countries all over the world,[4] and while reporting of histologic subtype-specific survival of lung cancer patients treated in cancer hospitals is also common,[5,6] reporting of this survival from population-based data is rare. With regard to SCLC status, however, this may be problematic for three reasons: cancer patients treated in cancer hospitals have a relatively better health status than those treated at general hospitals; survival reports from cancer hospitals are often restricted to patients who undergo surgery; and overall lung cancer survival from population-based data mainly reflects the survival of patients with NSCLC, given that NSCLC accounts for more than 80% of lung cancer cases.[7] For these reasons, overall lung cancer survival data might not be applicable to patients with SCLC.

Prognosis of cancer patients is modified by disease stage and treatment.[8] Treatment plans in patients with SCLC are commonly determined using a two-stage system originally introduced by the Veterans' Affairs Lung Study Group, together with the TNM staging system.[9,10] SCLC patients are classified into two stages, limited disease (LD) or extensive disease (ED), which are utilized for treatment selection. Tumor confined to the ipsilateral hemithorax and regional nodes is defined as LD, and tumor beyond the boundaries of LD is defined as ED. In general, patients with LD-SCLC are treated using multimodal treatment, while those with ED-SCLC receive systemic therapy.[11]

Address for correspondence. Isao Oze, MD, PhD, Division of Cancer Epidemiology and Prevention, Department of Preventive Medicine, Aichi Cancer Center Research Institute, 1-1 Kanokoden, Chikusa-ku, Nagoya 464-8681, Japan (e-mail: i_oze@aichi-cc.jp).

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SCLC treatment has changed over time. Around 1999, several clinical studies supported the efficacy of concurrent chemoradiotherapy and hyperfractionated radiotherapy for LD-SCLC.[12,13] The efficacy of new combination chemotherapy with cisplatin and irinotecan for Japanese patients with ED-SCLC was established in 2002.[14] In addition, new drugs for ED-SCLC, amrubicin and topotecan, were approved in Japan in 2002 and 2003, respectively.[15–17] Although these developments in SCLC treatment might have improved prognosis, scarce evidence for their impact is available based on population-based data.

Here, to determine specific survival of SCLC with consideration to disease stage and developments in treatment, we estimated recent trends in 10-year survival of patients with SCLC based on population-based data in Japan.

MATERIAL AND METHODS

Data source

This study was conducted using the framework of the Japanese Cancer Survival Information for Society (J-CANSIS) study. Details of the J-CANSIS study are provided elsewhere.[18] In brief, the J-CANSIS study aimed to analyze recent trends in cancer survival and report long-term survival based on population-based cancer registry data of six prefectures (Yamagata, Miyagi, Fukui, Niigata, Osaka, and Nagasaki) in Japan. These six registries provided a total of 98,475 lung cancer cases diagnosed between 1993 and 2006. The population covered in our study represents 13.4% of the total Japanese population and includes both urban and rural areas. These prefectural cancer registries have high data quality (% of death certificate only = 3.1–24.6%) and have long been used to estimate national statistics for cancer survival in Japan.[19] Morphologies of lung cancer were recorded using the morphology codes of the International Classification of Diseases for Oncology, Third Edition (ICD-O-3).[20] Data from cancer patients followed for 5 years or more were used. Patients were linked to the prefecture death certificate database to confirm their vital status. The Yamagata, Fukui, Osaka, and Nagasaki registries additionally confirm the vital status of patients using linkage to the residential database. We excluded data that were registered using death certificate only cases from the analysis.

Grouping of morphology was defined according to Cancer Incidence in Five Continents, Volume IX.[21] Morphology codes of 8041–8045 and 8246 were defined as SCLC, and all SCLC patients ($n = 10,911$) were included in the study. Lung cancer patients with other morphologies were excluded. Disease stage at diagnosis was categorized using a summary staging system.[22] LD-SCLC and ED-SCLC were defined using the Veterans Administration Lung Cancer Study Group (VALSG) staging system.[9] In short, SCLC confined to one hemithorax was defined as LD. Ipsilateral lymph node metastasis and contralateral hilar lymph node metastasis was defined as ED. LD-SCLC was defined as localized and regional stage on the summary staging system. ED-SCLC was defined as distant stage on the summary staging system. Localized and regional stages correspond to T1-2, N0-2, and M0 in the American Joint Committee of Cancer (AJCC) TNM staging system.

This study was approved by the ethics committee of Osaka Medical Center for Cancer and Cardiovascular Diseases (Osaka, Japan) in September 2013. Use of the data was approved by the six prefectural cancer registries.

Statistical analysis

We defined three periods (period 1, 1993–1998; period 2, 1999–2001; period 3, 2002–2006) to mirror the development of SCLC treatment. Elderly lung cancer patients were often defined as those who were aged 65, 70, or 75 years and older in clinical research. Therefore, age at diagnosis was classified into three groups: less than 65 years, between 65 and 74 years, and 75 years or older.

Trends in SCLC survival were assessed using relative survival (RS), because this is a standard method used to adjust for competing causes of death.[23] RS is the ratio of the observed (overall) survival and expected survival. The background mortality of cancer patients was derived using the complete national population life tables by birth year, age, and sex.[24] We estimated RS by applying the maximum likelihood method proposed by Esteve et al.[25] We calculated the 1-, 3-, 5-, and 10-year RS for patients diagnosed in period 1 and period 2 using a conventional approach (cohort approach). Instead of 10-year RS, 1-, 3-, and 5-year RS for patients diagnosed in period 3 were calculated using the cohort approach, because 10-year survival data for these patients were not available (Figure 1, black dash frame). One-, 3-, 5-, and 10-year RS for patients diagnosed in period 3 were estimated using the period approach. Long-term RS could be estimated using the period approach from recently followed-up data. Ten-year RS for patients diagnosed in period 3 (2002–2006) was estimated using the survival data for patients diagnosed between 1993 and 2006 and followed-up between 2002 and 2006 (Figure 1, gray dashed frame).

RS was compared using the excess hazards model,[26] a multivariate regression approach based on generalized linear models which adopts the Poisson assumption for the observed number of deaths. The excess hazards model is based on the idea that the total mortality hazard of cancer patients is decomposed into an *excess* hazard of death from cancer, and a hazard for other causes of death, derived from population life tables as background mortality of general populations. Period, sex, and age at diagnosis were included in the excess hazard model.

Using data of patients diagnosed in period 3, conditional 5-year survival was calculated. Conditional 5-year survival was 5-year survival with the pre-condition of having already survived a certain length of time (0 to 5 years in this report). Conditional 5-year survival for x-year survivors is calculated as follows: divide the (x+5)-year cumulative survival rate by the x-year cumulative survival, or calculate (x+5)-year cumulative survival, limited to the x-year survivors, in accordance with other studies.[27–30]

All analyses were conducted using STATA version 14.2 (StataCorp, College Station, TX, USA). The *strel* command in this software was used to calculate RS in both the cohort and period approaches.[31]

RESULTS

In total, 98,475 lung cancer patients, including 10,911 SCLC patients, were registered in the six prefectural cancer registries between 1993 and 2006. Proportions of SCLC in periods 1, 2 and 3 were 11.6%, 11.1%, and 10.7%, respectively. Characteristics of SCLC patients in the three periods are shown in Table 1. Proportions of female patients were approximately 18% throughout the periods. Proportions of elderly patients (aged ≥75 years) in periods 1, 2, and 3 were 25.2%, 29.1%, and 33.3%,

Year of Diagnosis	Year of follow-up																	
	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011
1993	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
1994		0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
1995			0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
1996				0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1997					0	1	2	3	4	5	6	7	8	9	10	11	12	13	14
1998						0	1	2	3	4	5	6	7	8	9	10	11	12	13
1999							0	1	2	3	4	5	6	7	8	9	10	11	12
2000								0	1	2	3	4	5	6	7	8	9	10	11
2001									0	1	2	3	4	5	6	7	8	9	10
2002										0	1	2	3	4	5	6	7	8	9
2003											0	1	2	3	4	5	6	7	8
2004												0	1	2	3	4	5	6	7
2005													0	1	2	3	4	5	6
2006														0	1	2	3	4	5

Figure 1. Patient data used in the survival analysis. Black figures indicate the data from six prefectural cancer registries, and the numbers within the cells indicate years of follow-up. Data in the black and gray solid frames were used to calculate 10-year relative survival by the cohort approach for patients diagnosed in period 1 (1993–1998) and period 2 (1999–2001), respectively. Data in the black dashed frame were used to calculate 5-year relative survival by the cohort approach for patients diagnosed in period 3 (2002–2006). Data in the gray dashed frame were used to calculate 10-year relative survival using period analysis for patients diagnosed in period 3 (2002–2006).

Table 1. Characteristics of study subjects

	1993–1998		1999–2001		2002–2006		Total	
	Number	%	Number	%	Number	%	Number	%
Sex								
Male	2,817	82.2	2,501	81.2	3,639	82.6	8,957	82.1
Female	610	17.8	579	18.8	765	17.4	1,954	17.9
Age, years								
≤64	1,093	31.9	842	27.3	1,169	26.5	3,104	28.4
65–74	1,469	42.9	1,341	43.5	1,770	40.2	4,580	42.0
≥75	865	25.2	897	29.1	1,465	33.3	3,227	29.6
Disease stage								
Limited disease (LD)	1,482	43.2	1,369	44.4	1,756	39.9	4,607	42.2
Extensive disease (ED)	1,469	42.9	1,371	44.5	2,203	50.0	5,043	46.2
Unknown	476	13.9	340	11.0	445	10.1	1,261	11.6
Total	3,427	100.0	3,080	100.0	4,404	100.0	10,911	100.0

respectively. The proportion of patients with ED-SCLC increased from 42.9% in period 1 to 50.0% in period 3.

Ten-year RS curves of each period by disease stage are shown in Figure 2 and Table 2. Five-year RS curves of both LD- and ED-SCLC patients in period 3 calculated using the cohort approach were similar to those estimated by the period approach. One-, 3-, 5-, and 10-year RSs of LD-SCLC patients in period 2 were better than those in period 1. The 10-year RS curve of LD-SCLC patients in period 3 estimated using the period approach was similar to that in period 2 estimated using the cohort approach. One- and 3-year RSs of ED-SCLC patients in period 3 were better than those in period 1, whereas 5- and 10-year RSs of ED-SCLC in period 1 were similar to those in period 3 estimated using the period approach. Ten-year RS curves in each period were similar between male and female patients with SCLC. RS of SCLC patients aged 75 years and more was approximately half that of patients aged less than 65 years in each period (eTable 1).

We estimated the EHR of SCLC patients' hazard of death from cancer within 5 years (Table 3). When stratified by disease stage, LD- and ED-SCLC showed similar trends. Excess mortality in periods 2 and 3 was significantly lower than that in period 1. Female LD-SCLC patients showed no statistically significant difference in mortality from male patients, whereas female ED-SCLC patients showed significantly better survival than male patients.

Conditional 5-year RS stratified by disease stage are shown in Figure 3. Conditional 5-year survival for patients with LD-SCLC increased from 21% at year 0 to 73% at year 5, while that in patients with ED-SCLC increased from 3% at year 0 to 53% at year 5. Because the 2-year RS of patients with ED-SCLC was 9.8%, confidence intervals for the conditional 5-year survival of ED-SCLC patients at years 3 to 5 are wide.

DISCUSSION

In this study, we found that the RS of patients with SCLC slightly improved between 1993 and 2006, despite increases in the number of elderly patients and relative proportion of ED-SCLC. This improvement in RS was confirmed after adjustment for period, sex, and age at diagnosis. To the best of our knowledge, this is the first study to show the RS of patients with SCLC stratified by disease stage using population-based data.

Among results, we found that the RS of patients with LD-SCLC in periods 2 and 3 were better than that in period 1. This improvement in survival was consistent with the develop-

Small Cell Lung Cancer Survival in Japan

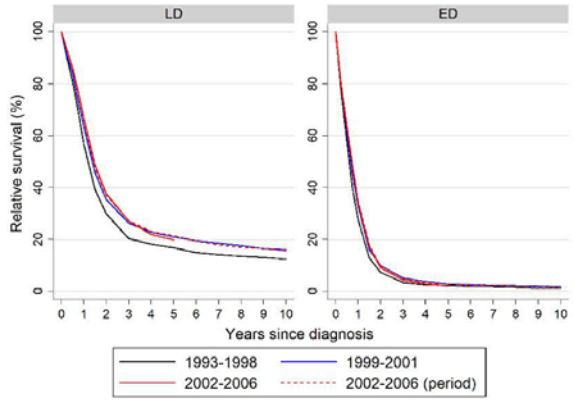

Figure 2. Ten year relative survival of patients with small-cell lung cancer. Relative survival was stratified by disease stage. ED, extensive disease; LD, limited disease.

Table 2. 1-, 3-, 5-, and 10-year relative survival of patients with SCLC stratified by disease stage

Relative survival (%)	Years since diagnosis							
	1		3		5		10	
	Survival	(95% CI)	Survival	(95% CI)	Survival	(95% CI)	Survival	(95% CI)
Limited Disease (LD)								
Period 1 (1993–1998)	56.8	(54.3–59.1)	20.3	(18.3–22.3)	16.8	(14.9–18.7)	12.4	(10.6–14.4)
Period 2 (1999–2001)	63.6	(60.5–66.6)	26.2	(23.4–29.1)	21.1	(18.4–23.8)	16.1	(13.5–18.8)
Period 3 (2002–2006)	66.9	(64.5–69.2)	27.0	(24.8–29.3)	19.9	(17.8–22.0)		
Period 3 (period[a])	66.2	(63.8–68.5)	27.2	(25.0–29.5)	21.4	(19.3–23.6)	15.6	(13.4–18.0)
Extensive Disease (ED)								
Period 1 (1993–1998)	27.7	(25.6–29.8)	3.4	(2.6–4.4)	2.3	(1.6–3.1)	1.2	(0.7–1.8)
Period 2 (1999–2001)	33.0	(30.1–35.9)	5.2	(3.9–6.7)	2.8	(1.9–4.0)	1.7	(1.0–2.9)
Period 3 (2002–2006)	34.3	(32.3–36.4)	4.3	(3.5–5.3)	2.0	(1.4–2.7)		
Period 3 (period[a])	34.8	(32.8–36.9)	5.0	(4.0–6.0)	2.7	(2.0–3.6)	1.4	(0.8–2.3)

CI, confidence interval; ED, extensive disease; LD, limited disease; SCLC, small-cell lung cancer.
[a]Relative survival and CIs were estimated using the period method. Survival data of patients followed between 2002 and 2006 were used.

Table 3. Excess hazard ratio (EHR) of death by excess mortality model stratified by disease stage

	Limited disease (LD)			Extensive disease (ED)		
	EHR	95% CI	*P* value	EHR	95% CI	*P* value
Period						
1993–1998	1	Reference		1	Reference	
1999–2001	0.84	0.77–0.92	<0.001	0.86	0.80–0.94	<0.001
2002–2006	0.77	0.72–0.84	<0.001	0.85	0.79–0.90	<0.001
Sex						
Male	1	Reference		1	Reference	
Female	1.04	0.95–1.13	0.401	0.92	0.85–0.99	0.028
Age at diagnosis, years						
≤64	1	Reference		1	Reference	
65–74	1.29	1.19–1.40	<0.001	1.23	1.15–1.31	<0.001
≥75	1.92	1.76–2.10	<0.001	1.71	1.58–1.85	<0.001

CI, confidence interval; EHR, excess hazard ratio.
Period, sex and age were included in the model.

ment of chemoradiotherapy.[12] A new chemoradiotherapy method, concurrent radiotherapy and hyperfractionated radiotherapy, improved the RS of patients with LD-SCLC diagnosed after 1997. LD-SCLC patients had a similar survival in period 3 to that in period 2. This seems consistent with the fact that no significant new treatment for LD-SCLC was developed during this time.

The improvement in ED-SCLC survival in periods 2 and 3 compared with period 1 was inconsistent with the development of chemotherapy. A clinical study in Japan showed that patients with ED-SCLC treated with the new combination of cisplatin and irinotecan had longer survival than those treated using standard chemotherapy with cisplatin and etoposide.[14] In a replication study, however, cisplatin and irinotecan showed no significant benefit compared with standard chemotherapy.[32–34] In addition, the higher rate of nonhematologic toxicity with the cisplatin and irinotecan regimen might decrease feasibility, and the new regimen might, therefore, have lacked impact on survival using population-based data. The RS of ED-SCLC patients in period 2 was better than that in period 1, despite no obvious improvement in ED-SCLC treatment. One reason might be the development of supportive care and palliative care. Total usage of opioids, a proxy for supportive care,[35] was 706 kg of morphine equivalent in Japan in 1995, rapidly increasing to 891 kg in 2000 and 2,696 kg

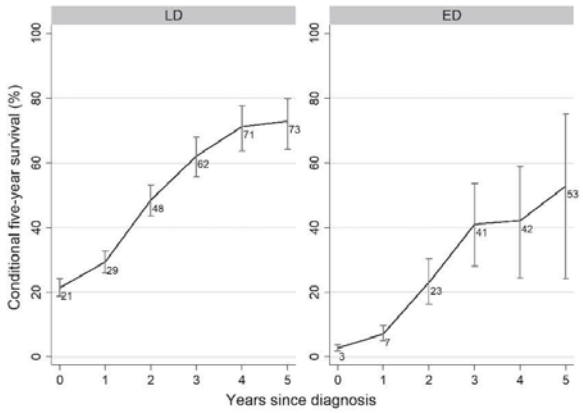

Figure 3. Conditional 5-year relative survival and 95% confidence intervals of SCLC patients stratified by disease stage. ED, extensive disease; LD, limited disease; SCLC, small-cell lung cancer.

in 2004.[36] Given that supportive care impacts the prognosis of patients with lung cancer, this increase in supportive care might have improved the prognosis of patients.[37]

The RS curves in period 2 were better than those in period 1 for both LD-SCLC and ED-SCLC. The RS curves in period 2 were similar to those in period 3 for both LD-SCLC and ED-SCLC. This similarity should be carefully considered because the improvement might have been due to stage migration. Improvements in diagnostic methods allow the detection of very small metastatic tumors. Patients with small distant metastasis would have been classified as LD in period 1. With the detection of small metastases with improved imaging, however, the patient would be diagnosed as ED. Movement of such patients with small metastases from LD to ED would improve the prognosis of LD patients, because their prognosis would be poorer than that of those without metastasis. Similarly, the prognosis of ED patients would be improved via the addition of patients with small metastases. The increased proportion of ED patients may support this hypothesis.

Conditional 5-year survival shows the conditional probability of surviving a further 5 years for cancer survivors.[38] It is a more informative way for survivors to see their evolving prognosis over time. Conditional 5-year survival was low in our patients with LD-SCLC compared with other malignancies.[18] Even 5 years post-diagnosis, conditional 5-year survival was 73%. The low conditional 5-year survival was mainly due to the poor prognosis of SCLC. In addition, the low conditional survival might be partly explained by the high proportion of heavy smokers among patients with SCLC.[39] Even SCLC patients with long survival may eventually die due to other cigarette-associated disease and comorbidities.

Lung cancer screening might be another potential factor to influence SCLC survival. Because of aggressive growth of SCLC, most SCLC cases were discovered as symptomatic cancers during the interval of annual lung cancer screening,[40] which suggests that lung cancer screening is unlikely to improve survival in patients with SCLC.[41] Even if SCLC could be screened effectively, it is less likely that screening affects stage-specific survival. Therefore, lung cancer screening programs were unlikely to affect the results of our study.

The strength of this study is its use of population-based cancer registry data. Because all SCLC incident cases in six prefectures were included, the study is unlikely to have suffered from the selection bias which confounds clinical trials and hospital-based cancer registries. A second strength was its large sample size. Most reports of SCLC survival have been derived from hospital-based studies.[5,42] The largest Japanese hospital-based lung cancer registry, the Japanese Joint Committee for Lung Cancer Registration, reported histology in specific lung cancer survival.[5] However, their study included only 243 SCLC cases versus 10,911 incident SCLC cases in our present study.

This study has a number of limitations. First, long-term survival was estimated using data from only six prefectural cancer registries. Second, data quality was not particularly high. The proportion of death certificate only cases among registries was 3.1% to 24.6%. The generalizability of the results should, therefore, be interpreted cautiously. Thanks to the enactment of the Cancer Registry Law in 2013, the quality of population-based cancer registry data will shortly improve.[43,44] This will allow new estimations of cancer survival with greater timeliness, longer follow-up, and inclusion of many more prefectures in Japan. Considering the decreasing trend in the incidence of SCLC,[45,46] analysis might require larger coverage to attain a stable estimation. Third, detailed information, such as treatment, comorbidity, and smoking status, was not available. These variables affect cancer survival, but the data are not fully collected in population-based cancer registries. Verification of the influence of these clinical factors on prognosis would require studies using detailed clinical data from hospital-based cancer registries.

In conclusion, we reported the 10-year RS and conditional survival of patients with LD- and ED-SCLC. RS after 1999 was better than that before 1998, although conditional survival was poor even among the patients with LD-SCLC. The forthcoming improvement in the quality and timeliness of cancer registry data in Japan will allow continuous survey using population-based data from many prefectures to estimate the progress of treatment.

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Conflicts of interest: None declared.

APPENDIX A. SUPPLEMENTARY DATA

Supplementary data related to this article can be found at https://doi.org/10.2188/jea.JE20180112.

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添付2

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RESEARCH ARTICLE

Cancer Medicine Open Access WILEY

Trends in the incidence of head and neck cancer by subsite between 1993 and 2015 in Japan

Daisuke Kawakita[1,2] | **Isao Oze**[1] | **Shinichi Iwasaki**[2] | **Tomohiro Matsuda**[3] | **Keitaro Matsuo**[1,4] | **Hidemi Ito**[5,6]

[1]Division of Cancer Epidemiology and Prevention, Department of Preventive Medicine, Aichi Cancer Center Research Institute, Nagoya, Japan

[2]Department of Otorhinolaryngology, Head and Neck Surgery, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan

[3]Division of International Collaborative Research, Center for Public Health Sciences, National Cancer Center, Tokyo, Japan

[4]Department of Epidemiology, Nagoya University Graduate School of Medicine, Nagoya, Japan

[5]Division of Cancer Information and Control, Department of Preventive Medicine, Aichi Cancer Center Research Institute, Nagoya, Japan

[6]Division of Descriptive Cancer Epidemiology, Nagoya University Graduate School of Medicine, Nagoya, Japan

Correspondence
Hidemi Ito, Division of Cancer Information and Control, Department of Preventive Medicine, Aichi Cancer Center Research Institute, 1-1 Kanokoden, Chikusa-ku, Nagoya, Aichi 464-8681, Japan.
Email: hidemi@aichi-cc.jp

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Abstract

Background: Tobacco use and alcohol consumption are still important risk factors for head and neck cancer (HNC) in developing countries, even though decreasing in tobacco prevalence. Recently, an increased incidence of oropharyngeal cancer due to human papilloma virus (HPV) infection has attracted attention in advanced countries, including the United States and Europe. However, few studies have evaluated trends in the incidence of HNC by subsite in Japan.

Methods: Accordingly, we evaluated these trends in Japan using data from population-based cancer registries. We compiled population-based incidence data from the Monitoring of Cancer Incidence in Japan Project, based on data from 19 population-based cancer registries. Number of incident cases and age-standardized incidence rates of HNC were estimated by subsite, namely lip, oral cavity, salivary glands, nasopharynx, oropharynx, hypopharynx, larynx, nasal and paranasal cavity, middle ear and NOS. Trends in agestandardized incidence rates were characterized using the Joinpoint analysis.

Results: Among both sexes, oral cavity cancer, salivary gland cancer, and oropharyngeal cancer showed an upward trend (oral cavity: annual percent change (APC) 1.2% for men and APC 1.9% for women; salivary gland: APC 2.2% for men and APC 3.1% for women; oropharynx: APC 5.0% for men and APC 7.6% for women). Additionally, hypopharyngeal cancer showed an upward trend for men (APC 4.1%), and nasopharyngeal cancer and laryngeal cancer showed a downward trend for men (nasopharynx: APC −2.7%; larynx: −1.1%).

Conclusions: These findings will assist in focusing on the individual prevention of HNC.

KEYWORDS
age-standardized incidence rate, annual percent change, head and neck cancer, subsite

1 | INTRODUCTION

Head and neck cancer (HNC) is the seventh most common cancer worldwide, and accounts for over 800,000 new cases annually.[1] HNC occurs in various subsites, including the lip, oral cavity, salivary glands, nasopharynx, oropharynx, hypopharynx, larynx, nasal and paranasal cavity, and ear. Indeed, the most common sites of incidence among HNC cases vary by geographic region, because the etiology of HNC is mainly lifestyle factors.[2–6] Tobacco use and alcohol consumption are still important risk factors for HNC in developing countries, even though decreasing in tobacco prevalence.[7] In contrast, the incidence of oropharyngeal cancer due to human papilloma virus (HPV) infection has been increasing in advanced countries, including United States and European countries.[8–10] Thus, an understanding of trends in the incidence of HNC by subsite is one of the most important aspects of management of this condition. To date, however, few studies have evaluated trends in the incidence of HNC by subsite in Japan.[11–13]

Here, we assessed the overall incidence of HNC among Japanese men and women between 1993 and 2015, and describe the distribution and trends in incidence rates of HNC at subsites.

2 | MATERIALS AND METHODS

2.1 | Populations

We used data from 19 population-based cancer registries in Kumamoto, Nagasaki, Saga, Yamaguchi, Hiroshima, Tottori, Osaka, Shiga, Aichi, Fukui, Niigata, Kanagawa, Chiba, Gunma, Tochigi, Ibaragi, Yamagata, Miyagi, and Aomori prefectural governments, all of which are members of the Monitoring of Cancer Incidence in Japan (MCIJ) project.[14] All 47 prefectural cancer registries in Japan submitted cancer incidence data to the Project. National statistics of cancer incidence in 2015 in Japan were observed using date submitted to the MCIJ project in 2015. First, we selected 41 prefectural cancer registries whose data quality for all cancers in 2015 met the following the standards in the MCIJ project 2015: (i) proportion of cases reported by death certificate only (DCO%: death certificate only) of less than 10%, (ii) proportion of cases first notified through death certificate (DCN%: death certificate notification) of less than 20%, (iii) and mortality to incidence ratio (M/I) of less than or equal to 0.5.[14] From these, we then selected the 19 registries above because they submitted data between 1993 and 2005 to the MCIJ project 2015.[14] The selected registries encompassed data for 44.6% of the total Japanese population in 2015.

2.2 | Disease coding

Topology codes of the International Classification of Diseases, Version 10 (ICD10) were grouped into 10 categories: lip (C00), oral cavity (C02-04, 05.0, 05.8, 05.9, 06), salivary glands (C07-08), nasopharynx (C11), oropharynx (C01, 05.1, 05.2, 09–10), hypopharynx (C12-13), larynx (C32), nasal and paranasal cavity (C30.0 and C31), middle ear (C30.1), and oral cavity or pharynx not otherwise specified (NOS) (C14). Epithelial malignancies (8000–8574, ICD-O-3) arising in the head and neck were included.

2.3 | Statistical methods

We estimated sex-specific incidence rates of each subsite per 100,000 person-years and 95% confidence intervals (CI). Each incidence rate was standardized by age-adjustment according to the Segi's world standard population.[15] In addition, the annual percent change (APC) was calculated using the Joinpoint regression analysis.[16,17] Briefly, the Joinpoint regression analysis is a statistical method for the analysis of change in trends over continuous segments of time. The significance of an increase or decrease within each segment was evaluated after identifying the best fitting model. In describing the trends, if changing less than or equal to 0.5% per year ($-0.5 \leq APC \leq 0.5$) and the APC was not statistically significant, we characterized it as stable. If changing more than 0.5% per year ($APC < -0.5$ or $APC > 0.5$) and the APC was not statistically significant, we characterized it as non-significant change. If changing with a statistically significant $APC > 0$, we characterized it as rising. If changing with a statistically significant $APC < 0$, we characterized it as falling. We estimated age-adjusted incidence rates with STATA version 16 (STATA Corporation). For the Joinpoint regression analysis, we used the Joinpoint Regression Program version 4.9.0.0 (US National Cancer Institute). For the Joinpoint regression

analysis, we considered that less than 0.05 of two-sided *p*-values were statistically significant.

3 | RESULTS

Table 1 shows estimated age-standardized incidence rates (ASRs) per 100,000 men and women for HNC according to subsite in 2015. The ASR of overall HNC was estimated as 12.42 per 100,000 men and 3.71 per 100,000 women. The leading subsite was oral cavity among both men and women (ASR: 3.40 per 100,000 men and 1.93 per 100,000 women). Among men, larynx was the second most common site, followed by hypopharynx (ASR: 2.82 per 100,000 men for larynx; 1.93 per 100,000 men for hypopharynx). Additionally, salivary gland was the second most common site among women, followed by oropharynx (ASR: 0.44 per 100,000 women for salivary gland; 0.41 per 100,000 women for oropharynx).

Figure 1, Table 2, Table S1, and Figure S1 showed the results of the Joinpoint regression analyses for HNC incidence trends according to subsite between 1993 and 2015. All HNC showed an upward trend between 1993 and 2015 among both men and women (APC 0.9%, 95% CI: 0.3% to 1.5%, for men; APC 2.1%, 95% CI: 1.2% to 3.0%, for women). Oral cavity cancer, salivary gland cancer, and oropharyngeal cancer showed an increasing trend during the study period among both men and women (oral cavity: APC 1.2%, 95% CI: 0.4% to 2.1%, for men and APC 1.9%, 95% CI: 0.8% to 3.1%, for women; salivary gland: APC 2.2%, 95% CI: 0.6% to 3.9%, for men and APC 3.1%, 95% CI: 0.5% to 5.8%%, for women; oropharynx: APC 5.0%, 95% CI: 3.8% to 6.2%, for men and APC 7.6%, 95% CI: 4.7% to 10.5%, for women). Among men, hypopharyngeal cancer showed an increasing trend (APC 4.1%, 95% CI: 2.5% to 5.7%). In addition, nasopharyngeal cancer and laryngeal cancer showed a downward trend for men (nasopharynx: APC −2.7%, 95% CI: −4.6% to −0.7%; larynx: APC −1.1%, 95% CI: −1.9% to −0.3%). We did not find a significant trend for nasal and paranasal cavity cancer.

Due to the small number of incidence cases, we performed the Joinpoint regression analysis for lip, middle ear and NOS cancer using the moving average of incidence rate in 3-year category. Middle ear cancer showed a decreasing trend for men (APC −2.2%, 95% CI; −4.4% to −0.1%, between 1994 and 2006 and APC −10.4%, 95% CI; −14.7% to −5.9%, between 2006 and 2014). We did not find a significant trend for cancer of lip and NOS.

4 | DISCUSSION

In this study, we investigated trends in HNC incidence and site-specific HNC incidence in a large Japanese population between 1993 and 2015. All HNC showed an increasing trend between 1993 and 2015 among both men and women. By subsite, increasing trends for men were observed for cancer of the oral cavity, salivary gland, oropharynx and hypopharynx, and for women with cancer of the oral cavity, salivary gland, and oropharynx. Additionally, decreasing trends for men were observed for cancer of the nasopharynx and larynx. To our best knowledge, this study is the first study to evaluate trends in HNC incidence according to subsite using data from Japanese population-based cancer registries.

With regard to all HNC, a steady downward trend after 1973 was shown in the United States.[18,19] In addition, oropharyngeal cancer showed an upward trend due to the

TABLE 1 Age-standardized incidence rates per 100,000 men and women for head and neck cancer by subsite in 2015

		Men		Women	
Subsite	**ICD10 code**	**ASR**	**%**	**ASR**	**%**
Overall		12.42		3.71	
Lip	C00	0.05	0.4	0.03	0.8
Oral cavity	C02-04, 05.0, 05.8, 05.9, 06	3.40	27.4	1.93	52.0
Salivary gland	C07, 08	0.68	5.5	0.44	11.8
Nasopharynx	C11	0.49	4.0	0.16	4.2
Oropharynx	C01, 05.1, 05.2, 09, 10	1.93	15.5	0.41	11.0
Hypopharynx	C12, 13	2.25	18.1	0.23	6.1
Larynx	C32	2.82	22.7	0.25	6.7
Nasal and paranasal cavity	C30.0, 31	0.71	5.7	0.25	6.7
Middle ear	C30.1	0.01	0.1	0.01	0.2
NOS	C14	0.07	0.6	0.02	0.5

Abbreviations: ASR, age-standardized incidence rate; ICD, International Classification of Diseases; NOS, oral cavity or pharynx not otherwise specified.

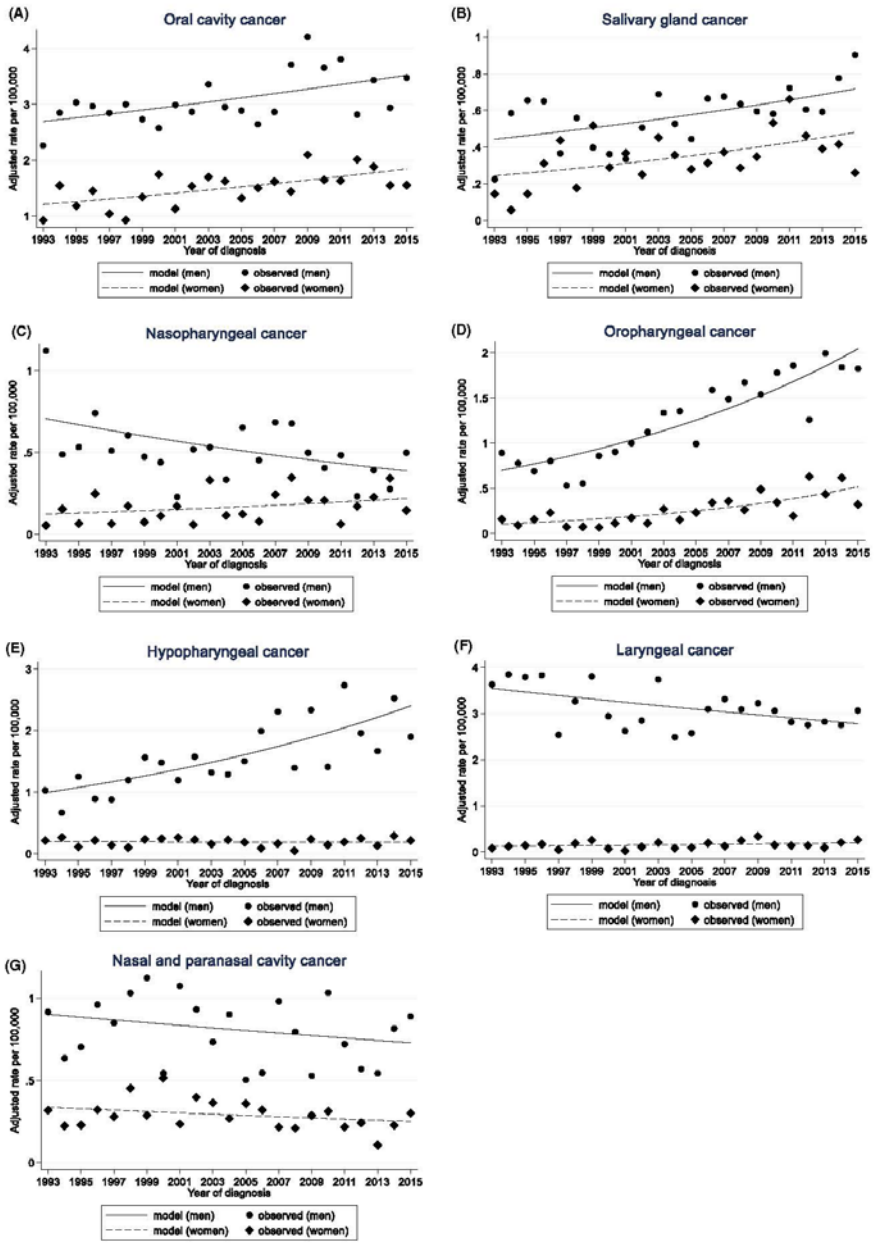

FIGURE 1 Joinpoint analysis for age-standardized (world population) incidence rates of oral cavity (A), salivary gland (B), nasopharyngeal (C), oropharyngeal (D), hypopharyngeal (E), laryngeal (F), nasal and paranasal cavity cancer (G) per 100,000 men and women

TABLE 2 Joinpoint analysis for head and neck cancer by subsite between 1993 and 2015

	Men			Women		
Subsite	Year	APC	95% CI	Year	APC	95% CI
Overall	1993–2015	0.9*	0.3, 1.5	1993–2015	2.1*	1.2, 3.0
Oral cavity	1993–2015	1.2*	0.4, 2.1	1993–2015	1.9*	0.8, 3.1
Salivary glands	1993–2015	2.2*	0.6, 3.9	1993–2015	3.1*	0.5, 5.8
Nasopharynx	1993–2015	−2.7*	−4.6, −0.7	1993–2015	2.6	−0.9, 6.3
Oropharynx	1993–2015	5.0*	3.8, 6.2	1993–2015	7.6*	4.7, 10.5
Hypopharynx	1993–2015	4.1*	2.5, 5.7	1993–2015	−0.4	−2.9, 2.2
Larynx	1993–2015	−1.1*	−1.9, −0.3	1993–2015	2.3	−1.1, 5.7
Nasal and paranasal cavity	1993–2015	−1.0	−2.5, 0.6	1993–2015	−1.3	−3.2, 0.5

Abbreviations: APC, estimated annual percent change (age-standardized to the world population); CI, confidence interval; NOS, oral cavity or pharynx not otherwise specified.

*APC is statistically significantly different from zero (two-sided $p < 0.05$).

increasing the prevalence of HPV infection, and laryngeal cancer showed a downward trend, which has been attributed to decreased rates of smoking.[9,18] In England, all HNC showed an upward trend between 2002 and 2011.[20] Additionally, HPV-associated sites had a significantly increasing trend while laryngeal cancer had a stable trend.[20] Consistent trends were seen in Denmark and the Netherlands.[21,22] On the other hand, in France, all HNC showed a downward trend for men and an upward trend for women between 1980 and 2012. This trend was consistent between HPV-associated and HPV-unassociated sites.[23] As for the Asia, Korea showed a downward trend for all HNC in men and a stable trend in women.[24,25] In addition, the overall incidence of HNC in Taiwan has continued to increase due to a rapid rise in oropharyngeal cancer.[25,26] In Thailand, although all HNC showed a downward trend, tongue cancer for both men and women and pharyngeal cancer for men had an upward trend.[27] In Japan, we found that all HNC had an upward trend in both men and women between 1993 and 2015. Consistent with the other countries, we found that oropharyngeal cancer had an upward trend for men and women in the study period. In addition, laryngeal cancer had a downward trend for men. Therefore, the more detailed investigation to clarify the impact of risk factors, including smoking and HPV infection, on the incidence of HNC in Japan is needed.

The increasing trend in HPV-positive oropharyngeal cancer in the United States and European countries is well known,[8,9,10,28] particularly given that HPV-positive oropharyngeal cancer cases have better survival than HPV-negative cases.[29] The prevalence of HPV infection in oropharyngeal cancer have been investigated in the Japanese population.[30–32] Hama reported that the prevalence of HPV infection was 50.3% (79/157) among Japanese oropharyngeal cancer cases.[30] In addition, Saito reported that the prevalence of p16-positive oropharyngeal squamous cell carcinoma cases increased from 15.2% between 2000 and 2003 to 33.3% between 2008 and 2011 at a single institution.[32] However, we were unable to find any cancer registry-based descriptive study of trends in oropharyngeal cancer incidence in Japan. In the present study, we showed that oropharyngeal cancer has been increasing for both men and women. Gillison reported that higher prevalence of oral HPV infection among men might be associated with the higher incidence of HPV-associated HNC.[33] Several possible mechanisms of this association have been suggested.[26,33–35] First, regarding sexual partners, higher number of men compared to women might increase the possibility of HPV infection in oral cavity. Second, female-to-male transmission of HPV through oral sex is more effective compared to male-to-female transmission. Finally, the seroprevalence of HPV is reportedly lower in men compared to women, and high levels of antibody against HPV have been shown to protect against subsequent HPV infection.[36,37] Unfortunately, we could not directly evaluate the association with these HPV infection-related factors because information on HPV infection was not available in this study, which is considered to be a limitation of this study. However, these factors might be associated with an upward trend in oropharyngeal cancer in Japan.

Tobacco smoking and alcohol drinking are the established risk factors for HNC.[2,6,38,39] Among subsites, laryngeal cancer is especially well known for its strong association with smoking.[2,39] The rate of smoking has been decreasing globally, including Japan,[2] although in contrast to the situation for men, the prevalence of current smoking among Japanese women has remained stable.[42,43] Despite this stable trend in women—extending back to the early 2000s, and thus covering the period in which prior smoking is expected to influence cancer incidence—laryngeal cancer did not show a downward

trend for women throughout the study period. This apparent discrepancy indicates the need to investigate the impact of other environmental or genetic risk factors on the incidence of laryngeal cancer among women in Japan.

Similarly, we found that hypopharyngeal cancer has increased among men. As for other countries, the Netherlands showed a downward trend for men and an upward trend for women between 1991 and 2010,[44] while in the United States, the incidence of hypopharyngeal cancer decreased from 1973 to 2010 with an APC of −2.0% every year.[45] Compared to other sites, hypopharyngeal cancer is more strongly associated with alcohol drinking than tobacco smoking, which is plausible considering the anatomical site.[6,46,47] In fact, the prevalence of habitual alcohol drinkers showed a slightly upward trend for men until early 2000s in Japan.[42] These trends might explain the observed increasing trends in hypopharyngeal cancer among men. It is known that hypopharyngeal cancer has the worst prognosis among HNC subtypes due to its frequent diagnosis at an already-advanced stage.[48] The upward trend in hypopharyngeal cancer should be noted, and focus should be placed on reducing the prevalence of the habitual alcohol drinking.

Among other findings, we found that salivary gland cancer shows an increasing trend among both men and women. Consistently with Japan, the United States showed that parotid gland cancer, which accounts for the majority of salivary gland cancers, rose steadily between 1973 and 2015 using the SEER database.[49,50] So far, several factors have been associated with the development of salivary gland cancer, including radiation or industrial exposure and smoking.[51–53] However, due to the rarity and distinct heterogeneous histopathological subtypes, risk factors for salivary gland cancer have not been established. These results identify a clear need to clarify the risk factors for salivary gland cancer in the Japanese population.

Finally, past data quality issues in the Japanese prefectural population-based cancer registries should be discussed. Data failed to meet international data quality standards in the early period but did do so in the later period (DCO: 26.2%, DCN: 29.1% and M/I: 1.81 in 2003, DCO: 3.8%, DCN: 6.9% and M/I: 2.38 in 2015).[14,54] This improvement in data quality standards was due to the selection of selected cancer-designated hospitals in 2007 to promote cancer control programs by the Ministry of Health, Labour, and Welfare. Candidate hospitals to have high-quality cancer registries were required,[55,56] which lead to an increase in the number of registrations and a dramatic decrease in the number of NOS cases, with detailed allocated to subsites. Therefore, the observed trends in incidence in our study might simply be an artifact representing an improvement in data quality.[14] Accordingly, we cannot totally deny this possibility because data from three of the population-based cancer registries with stable high quality during the observation period indicated a gradual upward trend in the HNC incidence in total and among subsites. However, consistent results in analyses limited to these three registries during the observation period might indicate that any bias due to the improvement in data quality would have had minimal impact on the observed trend in incidence. Trends for all HNC and subsites should be continuously monitored from 2016 using data from population-based cancer registries which meet international data quality standards.

In conclusion, we identified trends in HNC incidence by subsite between 1993 and 2015 in a large representative Japanese population based on population-based cancer registries. These trends might be due to changes in lifestyle factors in Japan. These results are crucial for the setting of public health priorities.

ETHICS STATEMENT

This paper has not been published in this or a substantially similar form (in print or electronically, including on a web site), nor accepted for publication elsewhere, nor is it under consideration by another publisher. This study was performed in accordance with the Declaration of Helsinki.

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CONFLICT OF INTEREST

All authors declare no conflict of interest associated with this study.

AUTHOR CONTRIBUTIONS

Daisuke Kawakita , Keitaro Matsuo, Hidemi Ito were involved in study design and data interpretation. All authors critically revised the report, commented on drafts of the manuscript, and approved the final report.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ORCID

Isao Oze https://orcid.org/0000-0002-0762-1147
Keitaro Matsuo https://orcid.org/0000-0003-1761-6314
Hidemi Ito https://orcid.org/0000-0002-8023-4581

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SUPPORTING INFORMATION

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添付3

CANCER EPIDEMIOLOGY

IJC

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

Yoshiaki Usui[1,2] | Hidemi Ito[1,3] | Yuriko Koyanagi[1] | Akiko Shibata[4] | Tomohiro Matsuda[4] | Kota Katanoda[5] | Yoshinobu Maeda[2] | Keitaro Matsuo[6,7]

[1]Division of Cancer Information and Control, Department of Preventive Medicine, Aichi Cancer Center, Nagoya, Japan

[2]Department of Hematology, Oncology and Respiratory Medicine, Okayama University Graduate School of Medicine, Dentistry and Pharmaceuticals Sciences, Okayama, Japan

[3]Division of Descriptive Cancer Epidemiology, Nagoya University Graduate School of Medicine, Nagoya, Japan

[4]Center for Cancer Registries, Center for Cancer Control and Information Services, National Cancer Center, Tokyo, Japan

[5]Division of Cancer Statistics Integration, Center for Cancer Control and Information Services, National Cancer Center, Tokyo, Japan

[6]Division of Cancer Epidemiology and Prevention, Department of Preventive Medicine, Aichi Cancer Center, Nagoya, Japan

[7]Department of Epidemiology, Nagoya University Graduate School of Medicine, Nagoya, Japan

Correspondence
Hidemi Ito, Division of Cancer Information and Control, Department of Preventive Medicine, Aichi Cancer Center, 1-1 Kanokoden, Chikusa-ku, Nagoya 464-8681, Japan.
Email: hidemi@aichi-cc.jp

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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

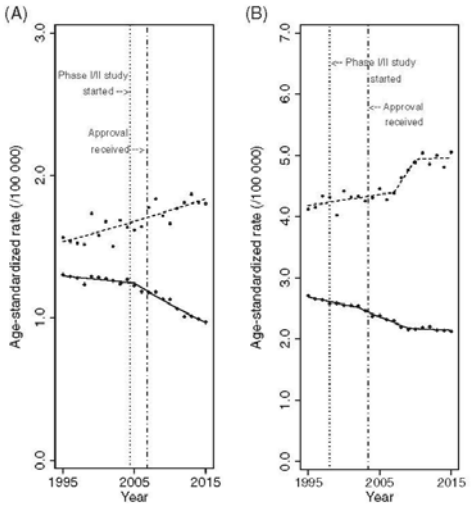

FIGURE 1 Overall trends in age-standardized mortality and incidence rate of multiple myeloma. Overall trends in age-standardized mortality and incidence rate of multiple myeloma in, A, Japan and B, the U.S. World standard population was applied. White circles indicate the observed incidence rate, *black 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

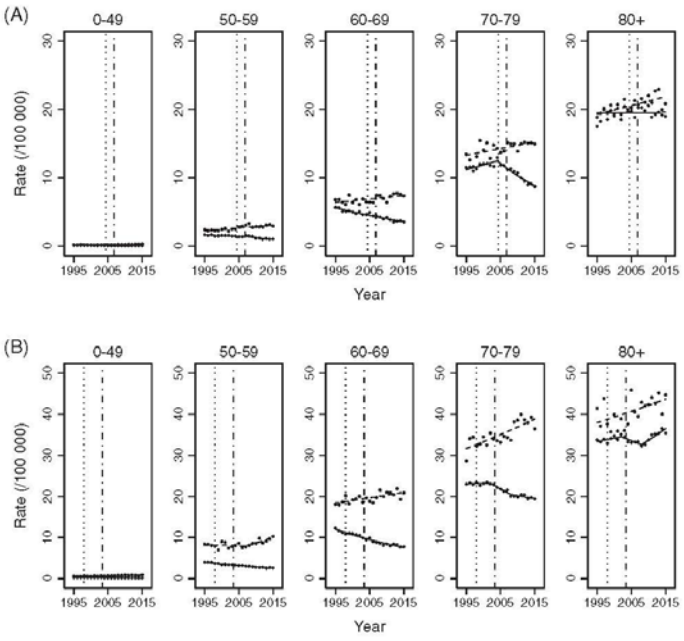

FIGURE 2 Age-specific trends in mortality and incidence rate of multiple myeloma. Age-specific mortality and incidence rate of multiple myeloma in, A, Japan and B, the U.S. White circles indicate the observed incidence rate, black diamonds indicate the observed mortality rate, and lines indicate modeled 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.

ORCID

Hidemi Ito https://orcid.org/0000-0002-8023-4581
Tomohiro Matsuda https://orcid.org/0000-0002-7311-1233
Keitaro Matsuo https://orcid.org/0000-0003-1761-6314

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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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RESEARCH ARTICLE Open Access

Prognostic impact of tumor location in colon cancer: the Monitoring of Cancer Incidence in Japan (MCIJ) project

Hiroko Nakagawa-Senda[1], Megumi Hori[2], Tomohiro Matsuda[3] and Hidemi Ito[4,5*]

Abstract

Background: Colorectal cancer (CRC) is globally one of the most common cancers. Although studies have found a significant prognostic impact of cancer location for right-sided colon cancers compared with those of the left-side, evidence is lacking in a Japanese population. Therefore, we investigated 5-year net survival in colon cancer by tumor site in a Japanese population.

Methods: Diagnoses obtained between 2006 and 2008 in 21 population-based cancer registries from the Monitoring of Cancer Incidence in Japan (MCIJ) project were used. Colon cancer patients were categorized as having right-sided (C18.0–18.4) or left-sided colon cancer (C18.5-C18.7). We calculated the 5-year net survival for subjects diagnosed from 2006 until 2008 by anatomical subsite according to sex, age groups, tumor stage at diagnosis. We applied the excess mortality model to calculate excess hazard ratios (EHRs) and 95% confidential intervals (CIs) with and without adjustment for age, sex and cancer stages to evaluate the effect of location of colon cancer.

Results: This study analyzed a total of 62,350 colon cancer subjects. Five-year net survivals for subjects with left- and right-sided colon cancer were 74.0% (95% CI, 73.4–74.7%) and 70.4% (95% CI, 69.7–71.0%), respectively. Compared with left-sided colon cancers, the EHR for right-sided colon cancers was 1.20 (95% CI, 1.16–1.25) after adjustment for age, sex and stage.

Conclusion: Our study found that the net survival for right-sided colon cancer was significantly lower than that for left-sided colon cancer. The anatomical site of cancer in the colon might be an important stratification factor in future studies of colon cancer.

Keywords: Population-based cancer registries, Colorectal cancer, Net survival, Anatomical subsite

Background

Colorectal cancer (CRC) is globally one of the most common cancers [1]. In 2012, the estimated incidence was 1,360,000 new patients and 694,000 deaths worldwide, accounting for 8.5% of total deaths [1]. The incidence and mortality of CRC have increased dramatically during the last several decades in a Japanese population [1–3]. In 2017, CRC was the most common cause of cancer death in women and the third-most common in men, with the 50,700 patients who died due to CRC accounting for 3.7% of total deaths in Japan [4].

The differentiation of colon cancer by anatomical subsite has received substantial attention over the past decade. The clinical and biological characteristics of CRC are different according to the anatomical subsites of the colon tumor [5, 6]. Recent studies have revealed that the frequency or incidence of right-sided colon cancer has increased during the past decade while that of left-sided colon or rectal cancer has remained stable or decreased [3, 7, 8]. Epidemiological studies have indicated that the impact of risk or protective factors on CRC might differ by colorectal anatomical subsites [9–13]. A recent systematic review noted that many studies have identified differences by anatomical subsite with regard to

* Correspondence: hidemi@aichi-cc.jp
[4]Division of Cancer Information and Control, Department of Preventive Medicine, Aichi Cancer Center Research Institute, 1-1 Kanokoden Chikusa-ku, Nagoya, Aichi 464-8681, Japan
[5]Department of Epidemiology, Nagoya University Graduate School of Medicine, Nagoya, Japan
Full list of author information is available at the end of the article

epidemiology, clinical presentation, pathology and genetic mutations [5]. These findings have in turn led to suggestions that the location of colon cancer may influence prognosis.

A number of epidemiological studies have reported the association between prognosis and cancer location in the colon. In 2016, a meta-analysis of 66 studies suggested that there was a significant prognostic impact of the tumor site, with an 18% increase in mortality risk for cancers arising from the right side [14]. Although most of these studies demonstrated poorer survival in right- than left-sided colon cancer [14–19], others are inconsistent [20, 21]. Contrary to these other studies, however, one recent population-based analysis suggested that the prognosis of left-sided colon cancer is worse than that of right-sided colon cancer [20]. In Japan, only a few studies have reported associations between cancer location in the colon and prognosis [17, 18, 21–23] namely poorer survival in right- than left-sided tumor [17, 18], better survival in right- than left-sided tumor [21] or no difference in survival between them [22, 23]. Thus, evidence to prove that the prognosis of colon cancer differs by side in a Japanese population is lacking.

Here, we aimed to investigate the net survival of patients with right- and left- sided colon cancers using data from population-based cancer registries in a Japanese population.

Methods

Using population-based cancer registries data from the Monitoring of Cancer Incidence in Japan (MCIJ) project, we analyzed colon cancer cases (ICD-10: C18.0–18.7) diagnosed from 2006 until 2008 in 21 population-based cancer registries (Aichi, Chiba, Ehime, Fukui, Fukushima, Gunma, Hiroshima, Ibaraki, Kanagawa, Kumamoto, Miyagi, Nagasaki, Niigata, Osaka, Okayama, Shiga, Shimane, Tochigi, Tottori, Yamagata and Yamanashi) in Japan. Cases were selected according to Japanese standards with regard to (i) proportion of cases reported by death certificate only (DCO%: death certificate only) of less than 25%, (ii) proportion of cases first notified through death certificate (DCN%: death certificate notification) of less than 30%, (iii) mortality to incidence ratio (M/I) of less than 0.67 [24], and (iv) percentage of lost to follow-up of < 5% or adopted linkage to a death certificate database to confirm the vital status of patients. We included those patients diagnosed in 2006–2008 and followed through Dec 31, 2013. Japanese population-based cancer registries start to follow patients at the date of diagnosis and do not register the date of operation or starting treatment. We excluded data from cases that were registered by death certificate only, were secondary multiple cancers, were in situ cases, and those in patients aged > 100 years. We also excluded data from cases that were registered by death certificate notification. The study included colon cancer cases (ICD-10: C18.0–18.7), cecum, C18.0; appendix, C18.1; ascending colon, C18.2; hepatic flexure of the colon, C18.3; transverse colon, C18.4; splenic flexure of the colon, C18.5; descending colon, and C18.6; and sigmoid colon, C18.7. Overlapping lesions of colon (C18.8) and those not otherwise specified (C18.9) were excluded. Colon cancer patients were further categorized into two groups, those with right-sided colon cancer (C18.0–18.4; cecum, appendix vermiformis, ascending colon, hepatic flexure of colon and transversal colon) and left-sided colon cancer (C18.5-C18.7; splenic flexure of colon, descending colon and sigmoid colon). With regard to the extent of disease, patients were categorized into the three disease stages of localized, regional and distant groups. Extent of disease was available in the Japanese population-based cancer registries. The Japanese staging system, extent of disease, was based on the Surveillance, Epidemiology, and End Results (SEER) staging criteria [25]. Extent of disease was unknown for 14.0% of subjects.

Statistical analysis

The frequency of related variables of patients by cancer locations was compared using the two sample t-test for continuous variables and the χ^2 test for categorical variables. We calculated 5-year net survival for colon cancer patients diagnosed from 2006 until 2008 by anatomical subsite according to sex, age group (< 40, 40–54, 55–69, ≥70), extent of disease at diagnosis (localized, regional or distant stages). Net survival is regarded as the survival that would be observed in the hypothetical situation that the only possible cause of death was cancer [26]. Net survival is calculated by following two methods: relative survival and cause-specific survival. The population-based cancer registries usually use relative survival to give estimates net survival [27]. We used the recently introduced Pohar Perme estimator [28] of net survival implemented with the program *strs* in Stata version 14.1. The complete national population life-tables by single year of age, sex and calendar year were used to derive the expected mortality rates. To assess the impact of anatomical location of the colon cancer on survival, the excess mortality model, a multivariate regression approach which adopts the flexible parametric model [29, 30] implemented with the *stpm2* function in Stata version 14.1 was used. We applied the excess mortality model to calculate excess hazard ratios (EHRs) and 95% confidential intervals (CIs) with and without adjustment for age, sex and cancer stages to assess the effect of the location of colon cancer. Cases in which the tumor stage was unknown were excluded when the excess mortality model was performed to adjust for tumor stage. The differences in survival rate with location of colon cancer between sex, age groups or tumor stages were statistically tested by including an interaction term into the excess mortality model. A two-sided *P*-value of <

0.05 was considered statistically significant. All statistical analyses were performed using Stata v. 14.1 (STATA Corporation, College Station, TX).

Results

Characteristics of subjects

Information on a total of 62,350 subjects diagnosed with colon cancer from 2006 until 2008 was analyzed, of whom 32,005 (51.4%) had right-sided disease and 30,345 (48.6%) had left-sided. The distribution of demographic variables among the subjects are shown in Table 1. Of these 62,350 patients, 53.8% were 70 years of age or older and 53.4% were male. With regard to tumor stages, most patients were diagnosed with localized disease (41.1%), followed by regional (27.7%), distant (17.3%) and stage unknown (14.0%). There were differences among tumor locations in age, sex and stage. Patients with right-sided cancer were significantly older (mean age 71.2 ± 11.5 vs 67.9 ± 11.4 years old), more likely to be female (52.3% vs 40.7%), and had a higher percentage of distant stage disease (18.0% vs 16.5%) ($p < 0.001$), compared to those with left-sided disease.

Survival analysis

Table 2 shows the 5-year net survival and estimated excess hazard ratios for colon cancer by sex, age group, disease stage and anatomic location. The 5-year net survival was lower in females than in males. Further, it decreased with increasing age after adjustment for sex and stage, and decreased with advancing stage after adjustment for sex and age. The 5-year net survival estimates for colon cancer by anatomical subsite are shown in Fig. 1, at 74.0% (95% CI, 73.4–74.7%) for subjects with left-sided colon cancer and 70.4% (95% CI, 69.7–71.0%) for right-sided disease. Compared with left-sided colon cancers, EHR for right-sided cancers was 1.20 (95% CI, 1.16–1.25) after adjustment for age, sex and tumor stage (Table 2).

The 5-year net survival for subjects with left- and right-sided colon cancer by sex, age group and tumor stage are also shown in Table 3. Five-year net survival for subjects with left- and right-sided disease were 74.5% (95% CI, 73.6–75.3%) and 73.2% (95% CI, 72.2–74.2%) for males, and 73.4% (95% CI, 72.4–74.3%) and 67.8% (95% CI, 66.9–68.7%) for females, respectively. Compared with left-sided disease, EHRs for right-sided disease were 1.19 (95% CI, 1.14–1.26) for males and 1.19 (95% CI, 1.13–1.26) for females after adjustment for age and stage. No heterogeneity was found between sexes ($P = 0.39$). With regard to age groups, 5-year net survival was lower for right-sided than left-sided disease in all age groups (Additional file 1: Figure S1A-D). Compared with left-sided cancers, EHRs for right-sided cancers were 1.09 (95% CI, 0.84–1.43) for age less than 40 years, 1.32 (95% CI, 1.18–1.48) for age 40–54 years, 1.15 (95% CI, 1.08–1.21) for age 55–70 years, and 1.26 (95% CI, 1.19–1.33) for age ≥ 70 years, respectively, after adjustment for sex and stage. Statistically marginal heterogeneity was found among these age groups ($P = 0.05$). Survival differences by anatomic subsite were observed for those aged 40 or over, whereas significant difference was not observed for those aged less than 40 years. By stage, 5-year net survival for right-sided disease was also lower than that for left-sided disease in regional and distant disease but higher in localized disease (Additional file 2: Figure S2A-C). EHRs for right-sided colon cancers, compared with left-sided, were 0.74 (95% CI, 0.60–0.90) for stage localized, 1.25 (95% CI,1.17–1.34) for stage regional, and 1.20 (95% CI, 1.15–1.25) for stage distant, respectively, after adjustment for sex and age. Heterogeneity was marginally significant among stages ($P = 0.07$).

Table 1 Patient characteristics

	Total (N=62,350)		Right-sided Cancer (N=32,005)		Left-sided Cancer (N=30,345)		
	N	%	N	%	N	%	p[a]
Age groups (years old)							
<40	867	1.4	409	1.3	458	1.5	<0.001
40-55	5,067	8.1	2,055	6.4	3,012	9.9	
55-70	22,879	36.7	10,403	32.5	12,476	41.1	
≥70	33,537	53.8	19,138	59.8	14,399	47.5	
Mean Age ± SD (years)	69.6 ± 11.6		71.2 ± 11.5		67.9 ± 11.4		<0.001[b]
Gender							
Male	33,274	53.4	15,268	47.7	18,006	59.3	<0.001
Female	29,076	46.6	16,737	52.3	12,339	40.7	
Stage							
Localized	25,603	41.1	12,575	39.3	13,028	42.9	<0.001
Regional	17,265	27.7	9,324	29.1	7,941	26.2	
Distant	10,761	17.3	5,756	18.0	5,005	16.5	
Missing	8,721	14.0	4,350	13. 6	4,371	14.4	

[a] Chi-Square test
[b] Two-sample t-test

Table 2 5-year net survival (%) and estimated excess hazard ratios for colon cancer by sex, age, group, stage and subsite, Japan, 2006-2008

	n	5-year net survival (%)	(95%CI)	EHRs	(95%CI)	*P*-value	*p* for trend
Overall, Colon Cancer	62350	72.1	71.7-72.6				
Sex[a]							
Male	33274	73.9	73.2-74.5	1.00	Reference		
Female	29076	70.1	69.5-70.8	1.05	1.01-1.08	0.012	
Age group[b]							
Age <40	867	68.8	65.7-72.0	1.00	Reference		
Age 40-54	5067	72.5	71.2-73.8	0.98	0.85-1.13	0.8	
Age 55-70	22879	74.8	74.2-75.4	1.04	0.91-1.19	0.55	
Age ≥70	33537	70.4	69.6-71.1	1.5	1.31-1.71	<0.001	<0.001
Stage[c]							
Localized	25603	97.1	96.5-97.7	1.00	Reference		
Regional	17265	73.4	72.5-74.3	7.36	6.60-8.20	<0.001	
Distance	10751	16.2	14.7-16.2	45.5	40.9-50.6	<0.001	<0.001
Subsite[d]							
Left-sided cancer	30345	74.0	73.4-74.7	1.00	Reference		
Right-sided cancer	32005	70.4	69.7-71.0	1.20	1.16-1.25	<0.001	

[a] Multivariate model adjusted for age and stages.
[b] Multivariate model adjusted for sex and stages.
[c] Multivariate model adjusted for sex and age.
[d] Multivariate model adjusted for age, sex and stages.

The results by age group and stage were consistent between the sexes when stratified by sex (Additional file 3: Table S1 and Additional file 4: Table S2).

Discussion

In this study, we showed that survival of subjects with right-sided colon cancer was lower than that of subjects with left-sided disease with assessment for adjusted EHRs. On stratification by age group, survival for right-sided disease was lower than that for left-sided disease in those aged 40 years or over, with assessment for adjusted EHRs. On stratification by tumor stage, survival for right-sided colon cancer was significantly lower than for left sided disease in regional and distant stage disease, but higher in localized disease. To our understanding, this is the first study to evaluate population-based

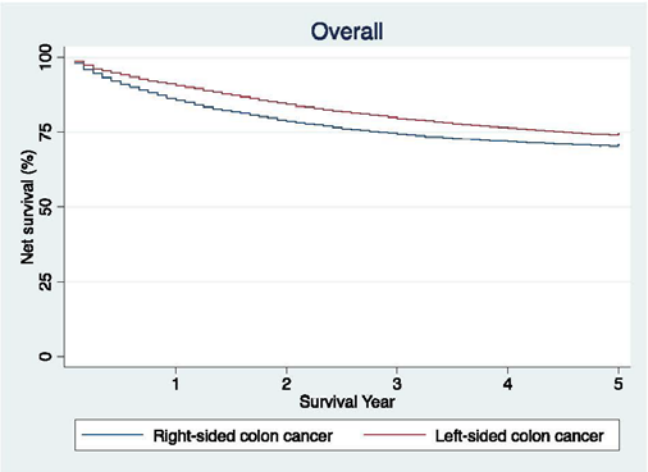

Fig. 1 5-year net survival for patients with right- and left-sided colon cancer. Net survival rates up to 5 years were shown in blue for right-sided colon cancer and in red for left-sided colon cancer

Table 3 5-year net survival (%) and estimated excess hazard ratios for colon cancer by subsite according to sex, age group and stage subsites, Japan, 2006-2008

	n	5-year net survival (%)	(95%CI)	EHRs	(95%CI)	*P-value*
Overall, Colon Cancer	62350	72.1	71.7-72.6			
Sex[a]						
Male						
Left-sided cancer	18006	74.5	73.6-75.3	1.00	Reference	
Right-sided cancer	15268	73.2	72.2-74.2	1.19	1.14-1.26	<0.001
Female						
Left-sided cancer	12339	73.4	72.4-74.3	1.00	Reference	
Right-sided cancer	16737	67.8	66.9-68.7	1.19	1.13-1.26	<0.001
P for heterogeneity by sex						0.39
Age group[b]						
Age <40						
Left-sided cancer	458	72.6	68.4-76.8	1.00	Reference	
Right-sided cancer	409	64.6	59.9-69.3	1.09	0.84-1.43	0.50
Age 40-54						
Left-sided cancer	3012	76.2	74.6-77.8	1.00	Reference	
Right-sided cancer	2055	67.2	65.1-69.3	1.32	1.18-1.48	<0.001
Age 55-70						
Left-sided cancer	12476	76.5	75.7-77.4	1.00	Reference	
Right-sided cancer	10403	72.7	71.8-73.6	1.15	1.08-1.21	<0.001
Age >70						
Left-sided cancer	14399	71.5	70.4-72.6	1.00	Reference	
Right-sided cancer	19138	69.5	68.5-70.5	1.26	1.19-1.33	<0.001
P for heterogeneity by age group						0.05
Stage[c]						
Localized						
Left-sided cancer	13028	95.9	95.1-96.7	1.00	Reference	
Right-sided cancer	12575	98.4	97.5-99.3	0.74	0.60-0.90	0.003
Regional						
Left-sided cancer	7941	76.8	75.6-78.1	1.00	Reference	
Right-sided cancer	9324	70.5	69.2-71.7	1.25	1.17-1.34	<0.001
Distance						
Left-sided cancer	5005	17.7	16.5-18.8	1.00	Reference	
Right-sided cancer	5756	13.5	12.6-14.5	1.20	1.15-1.25	<0.001
P for heterogeneity by stage						0.07

[a] Multivariate model adjusted for age and extent of disease.
[b] Multivariate model adjusted for age, sex and extent of disease.
[c] Multivariate model adjusted for sex and age.
[d] Multivariate model adjusted for age, sex and extent of disease.

cancer registry data using the unbiased Pohar Perme estimator of net survival to assess the effect of anatomical subsite on survival of colon cancer patients. Among previous studies on the association between the location and prognosis, a meta-analysis study reported that patients with right-sided colon cancers had an 18% increase in mortality risk and that this was independent of stage [14], which is similar to our result. Analyses using SEER data found that right-sided colon cancers were associated with a 4% increased risk of death compared with cancers of left-sided cases after adjustment for confounders [15]. However, a more recent analysis using the SEER database provided evidence that while right-sided cancer patients were associated with worse overall survival than left-sided disease patients, this relationship was reversed after propensity score matching, rendering the prognosis of cancers with right-sided better overall [20]. The authors speculated that differences among confounders that could not be adjusted for in multivariate regression analysis caused this reversal of results.

Differences in distribution by stage and age have an important effect on survival rate [20, 31]. Patients with a more advanced stage and older age at diagnosis had a greater increase in mortality risk [20, 31]. Compared with those aged < 40 years, hazard ratios for overall mortality were 1.20 (95% CI,1.12–1.28) for age 50–64 years, 2.30 (95% CI, 2.15–2.45) for age 65–79 years, and 5.10 (95% CI, 4.77–5.47) for age ≥ 80 years, respectively [20]. For this reason, we estimated the difference in survival by anatomical subsite with adjustment for stage and age groups. We confirmed that anatomical subsite was an independent prognostic factor for patients with colon cancer. Subsites within the colorectum are derived from distinct embryonic origins [5]. The survival differences between right- and left-sided colon cancer may have resulted from differences between subsites in epidemiology, genetic mutations, pathology and clinical features [5].

Epidemiological analyses of data from Japanese cancer registries and SEER have shown that incidence rate trends for proximal colon cancer differ from those of distal disease [3, 8]. Epidemiological studies found evidence that the impact of risk factors for CRC, including low physical activity and meat consumption, and protective factors, including coffee intake and aspirin use, differ by anatomical subsite [9–13]. Differences in gene expression between cancers in right- and left-sided colon have been evaluated: while right-sided cancers are characterized by *BRAF* mutation, high microsatellite instability (MSI), and CpG island methylation [32–34], left-sided cancers frequently have p53 and *KRAS* mutation [35]. BRAF mutations are a part of the RAS-RAF-MAP2K (MEK)-MAPK signaling pathway. *BRAF* mutation cancers were associated with worse overall survival than wild-type cancers [32, 33, 36]. CpG island methylation-positive tumors showed significantly worse outcomes than those with negative tumors [34]. These findings are consistent with our result. Patients with MSI-positive cancers nevertheless show better survival than those with cancers exhibiting microsatellite stability (MSS) [37], which is inconsistent with our results. Only a few studies have evaluated the combined impact of CpG island methylation, BRAF mutation status and MSI status on survival for colon cancer [38]. The mechanism of the difference in survival by location of colon cancer warrants further study. We found that survival was significantly lower for right-sided disease than for left-sided disease in patients aged ≥40. Although we observed no significant difference among those aged less than 40 years, and that the association was not statistically significant, the point estimates for the effect measures showed the same direction, with EHRs of more than 1.0. The lower survival in right-sided colon cancer might be robust in all age groups.

Our findings suggest that the anatomical site of colon cancer might be a crucial factor in establishing prognosis, particularly in advanced-stage disease. Prognosis for right-sided colon cancers was worse in stage III or IV according to the American Joint Commission on Cancer (AJCC), but did not differ or was better in AJCC stage I or II [15, 16, 19], which is consistent with our results. In Japan, while a few hospital-based studies have appeared [17, 18, 21–23], we are unaware of any study which has used population-based data to examine the association between the location and prognosis of colon cancer. The prognosis for cancer in the right-sided of the colon is worse than for disease in the leftside in stage III [17] and IV colon cancer [18], but better in stage I [21]. Our present results are consistent with these findings. In contrast, two other studies reported that no difference was observed in prognosis between cancers in right-sided and left-sided colon [22, 23].

The reasons for this inconsistent association between survival and anatomical cancer location by disease stage is not clear and warrants further study. One possibility might relate to cancer biology such as MSI status. MSI-positive tumors, which are mainly seen in right-sided colon, have been associated with improved prognosis [39]. MSI has a favorable stage profile. This inconsistent association might owe to the difference in the percentage of MSI-positive colon cancers according to stage [16]: MSI positivity in right-sided colon cancers was most frequent in stage II cancers, and less frequent in the order of stage III and stage IV disease [40]. Because MSI is predominantly seen in colon cancers of the right side, we assume that earlier stage right-sided disease could have a higher frequency of MSI positivity than left-sided disease at the same stage, but that this difference diminishes with increasing stage. In contrast, CpG island methylation and BRAF mutation do not appear to have a favorable stage profile. This may cause the inconsistent association seen between survival and tumor location by stage. To our understanding, however, no study has yet investigated the percentage of MSI-positive tumors according to cancer location and stage, or the influence of CpG island methylation, MSI status and BRAF mutation status in combination on survival by stage and subsite for colon cancer. The reason for the inconsistency in survival therefore remains unclear, and warrant further study.

This study has several strengths. First, we examined survival in colon cancers by anatomical subsites using data from a large population-based cancer registry in Japan. The population of the 21 prefectures was 60,117,000 in 2006, accounting for 47.1% of the total Japanese population. The use of population-based data allowed us to evaluate the actual prognostic effect of anatomical subsites in people with heterogeneous

backgrounds in the general population. Second, we calculated net survival with the newly introduced Pohar Perme estimator to show unbiased net survival. This estimator provides findings that are unaffected by deaths not related to this cancer, and is therefore the preferred standard for estimating net survival [41]. In addition, we applied the recently introduced flexible parametric model to evaluate the impacts of anatomical subsites of colon cancer in survival. Although Poisson regression models are popular, the recently developed flexible parametric model, first proposed by Royston and Parmar [29] and applied to relative survival model by Nelson et al. [30], has a number of advantages. First, it offers smooth estimates of excess mortality rates and relative survival on the log cumulative excess hazard scale through the use of restricted cubic splines. Other advantages include the ability to model time on a continuous scale, the provision of hazard functions and survival in an analytical manner, and the elimination of need for the use of split-time data [30].

This study also has several limitations. First, information on family history, performance status and comorbidities are not available in the MCIJ dataset. These factors might play a role in patient outcome, albeit to an unclear extent. Second, we can not obtain information on *BRAF* mutation, MSI, CpG island methylation and chemotherapeutic treatment from the MCIJ data. Since the middle of the 2000's, oxaliplatin with a fluoropyrimidine has been standard adjuvant chemotherapy for patients with stage III colon cancer, and is suggested to improve overall survival [42]. Information on adjuvant chemotherapy in the colon cancer patients with stage III also can not be ascertained from the MCIJ data, and we were unable to adjust for the use of adjuvant chemotherapy in this study. In addition, only extent of disease, and not specific stage groupings, was available in the Japanese population-based cancer registries. Furthermore, 14% of the subjects were diagnosed with stage unknown. However, because the proportion of stage unknown patients did not differ among the anatomical subsites, we believe that the effects of this stage unknown status are likely small.

Finally, the Japanese population-based cancer registries had issues with quality during the study period, and failed to meet data quality for international standards for the proportion of death-certificate-only. When hospitals do not report cancer patients and the patients survive, the assumption will be biased and survival rates might be underestimated. In addition, inclusion of death certificate notification cases in cases of death will also cause bias, and survival might be underestimated. For these reasons, we excluded data for cases that were registered by death certificate notification. Enactment of the new Promotion of Cancer Registries Law in 2016 will bring about an improvement in the data quality.

Conclusions

This study revealed the net survival for colon cancer by anatomical subsite using large population-based cancer registries data in a Japanese population. Net survival for right-sided colon cancer was significantly lower than that for left-sided disease. This finding suggests that right-sided colon cancer might be biologically more aggressive than left-sided colon cancer. Determining or comparing the biological profiles of colon cancers between right- and left-sided, including genetic changes, will elucidate the underlying mechanism. Anatomical site of cancer in the colon might suggest crucial stratification factors for future studies of colon cancer.

Additional files

Additional file 1: Figure S1. A. 5-year net survivals for patients with right- and left-sided colon cancer in those aged less than 40 years old. B 5-year net survivals for patients with right- and left-sided colon cancer in those aged 40–54 years old. C 5-year net survivals for patients with right- and left-sided colon cancer in those aged 55–70 years old. D 5-year net survivals for patients with right- and left-sided colon cancer in those aged > 70 years old. (ZIP 186 kb)

Additional file 2: Figure S2. A. 5-year net survivals for patients with right- and left-sided colon cancer in stage localized. B 5-year net survivals for patients with right- and left-sided colon cancer in stage regional. C 5-year net survival for patients with right- and left-sided colon cancer in stage distant. (ZIP 139 kb)

Additional file 3: Table S1. 5-year net survival (%) and estimated excess hazard ratios for colon cancer by subsite according to age group and stage subsites, Japan, 2006–2008, for males. (DOCX 216 kb)

Additional file 4: Table S2. 5-year net survival (%) and estimated excess hazard ratios for colon cancer by subsite according to age group and stage subsites, Japan, 2006–2008, for females. (DOCX 218 kb)

Abbreviations

95% CI: 95% Confidential interval; AJCC: American Joint Commission on Cancer; CRC: Colorectal cancer; DCN: Death certificate notification; DCO: Death certificate only; EHRs: Excess hazard ratios; M/I: Mortality to incidence; MCIJ: The Monitoring of Cancer Incidence in Japan; MSI: Microsatellite instability; MSS: Microsatellite stability; SEER: The Surveillance, Epidemiology, and End Results

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Availability of data and materials

The datasets used and analyzed in this study are not publicly available due the data generated for the reporting and monitoring cancer incidence by MCIJ but available only to the research members of MCIJ on reasonable request.

Authors' contributions
HNS is responsible for developing the study concept, performing data analysis, writing the draft of the paper, interpretation and final approval of present article. MH and TM managed and coordinated the data, and are responsible for revision and final approval of present article. HI is responsible for developing the study concept, interpretation and revision of the manuscript, and had final responsibility for the decision to submit for publication. All authors of this paper have read and approved of the final version of the manuscript.

Ethics approval and consent to participate
It is the policy of Japanese Cancer Registries to provide de-identified data to investigators for research purposes. As such the Monitoring of Cancer Incidence in Japan obtained the data to estimate the cancer incidence or survival from the registries. Informed consent was not necessary as in the "Notice from the Director of the Health Service Bureau of the Ministry of Health, Labour and Welfare", population-based cancer registry tasks were specified as corresponding to "improving public health", an exception as provided in the Private Information Protection Law, and the "Guidelines for the Appropriate Handing of Personal Information by Medical and Care-related Enterprises" confirmed the policy. This study was approved by the Research Ethics Committee in the National Cancer Center in Japan (Research Ethics Committee reference 2004–061, confirmed on 24 November 2004).

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

Publisher's Note

Author details
[1]Department of Public Health, Nagoya City University Graduate School of Medical Science, Nagoya, Japan. [2]Division of Cancer Statistics Integration, Center for Cancer Control and Information Services, National Cancer Center, Tokyo, Japan. [3]Division of Surveillance, Center for Cancer Control and Information Service, National Cancer Center, Tokyo, Japan. [4]Division of Cancer Information and Control, Department of Preventive Medicine, Aichi Cancer Center Research Institute, 1-1 Kanokoden Chikusa-ku, Nagoya, Aichi 464-8681, Japan. [5]Department of Epidemiology, Nagoya University Graduate School of Medicine, Nagoya, Japan.

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