労災疾病臨床研究事業費補助金

化学物質の有害性評価を加速するための国内疫学的サーベイランス手法の開発

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平成 29 年度～令和元年度　総合研究報告書

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I 総合研究報告書

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研究要旨：近年、わが国では化学工業製造従事者の膀胱がんや、印刷業者の胆管がんなど、今まで知られていなかった化学物質の有害性による職業性がんの発生が続いている。しかし、現在のところ、「どのような業種・職種でどのような疾病や死因が多いか」など、幅広い業種・職種を網羅的に探索し状況を把握する手法が開発されていない。そこで、本研究では、既存の大規模医療データ等を用いて、産業・職業ごとのがん及びその他の疾病の過剰リスクに関わる網羅的なサーベイランス手法を開発し、それをもとに特定の化学物質曝露との関連が疑われる疾病の同定や予後の解析につなげていくことを目的とする。

3 年間の研究の初年度（平成 29 年度）は、主な研究として腎細胞がんに焦点をあてた。また、研究分担者や研究協力者らとともに、幅広い業種・職種を対象にして種々のがん種の罹患状況や予後について網羅的、探索的な検討を行った。2 年度（平成 30 年度）は、幅広い職業・産業から、化学物質を扱っているかどうかを同定する手法と、化学物質への曝露とがん発症リスクと関連があるかどうかを、がん全体および尿路上皮がん、胆管がんにおいて評価した。また、職業と各種がん発症のリスクの関連を網羅的に解析した。さらに、わが国の一般環境における化学物質曝露と関連すると考えられる PRTR（Pollutant Release and Transfer Register：化学物質排出移動量届出制度）制度に基づく排出量・移動量の都道府県別の経年集計と、悪性新生物の主な部位別にみた都道府県別の標準化死亡比（standardized mortality ratio：SMR）の算出を行って関連を検討した。3 年度（令和元年度）は、がんに次ぐ死因第 2 位である循環器疾患を取り上げ、職業と循環器疾患発症のリスクの関連について網羅的な解析を実施した。また、比較参考例として、海外の病職歴データベースについて文献調査を行った。分担研究においては、使用した大規模医療データベースの一部対象者についてカルテ（診療録）レビューや病理診断記録の確認などを行った。有害物質曝露による発がんの病因論検討については 3 年間とおして実施した。

大規模医療データとして主に用いたのは、独立行政法人労働者健康安全機構が保有する約 650 万件（研究開始時点）の入院患者病職歴調査データベース（病職歴調査データベース、ICOD-R）である。本研究では、上記データベースの最長職業を取り上げ、日本標準職業分類 JSOC および日本標準産業分類 JSIC を基に 4 つの職業（ブルーカラー職、サービス職、専門職、管理職）、3 つの産業（ブルーカラー産業、サービス産業、ホワイトカラー産業）などの新たな分類を行って、網羅的解析に使用した。

平成 29 年度の研究からは、男性において、ブルーカラー産業のブルーカラー職従事者と比べると、全ての産業で職業地位の高い人（専門職や管理職）で腎細胞がんのリスクの高いことが示された。さらに詳細な解析から、高血圧、糖尿病、肥満等のストレス関連因子を通じて、職業地位の高い人の腎細胞がんのリスクが上昇する経路が示唆された。また、分担研究からは、第一次産業でいくつかのがん種に対するオッズ比が他の業種よりやや低く、逆に第三次産業でやや高い傾向が示された。地域がん登録データベースを用いた解析からは、胆管がんの予後の改善と予後に関連する要因を明らかにした。

平成 30 年度の研究では、特殊健康診断の受診の有無を化学物質曝露の代理指標とした分析を行ったが、化学物質曝露とがんの罹患リスク上昇との関連は見られなかった。他方、化学物質の曝露とは直接の関係はないが、わが国の男性のがんにおいて、職業と各がん罹患のリスクの間に一定の関連のあることを初めて明らかにした。特に専門職や管理職従事者に注目することで、日本人で頻度の高い胃がん、肺がん、肝臓がん、食道がん、膀胱がん、悪性リンパ腫において、専門職や管理職従事者の罹患リスクの低いことを明らかにした。分担研究では、産業分野によってがん罹患リスクの異なる可能性が示唆された。

令和元年度の研究では、循環器疾患に注目したことで、わが国の専門職/管理職で心血管疾患の罹患リスクが高く、脳血管疾患のリスクが相対的に低いという可能性が示唆された。分担研究では、化学物質曝露機会の多い製造業に限定した詳細な分析から、製造業種内でのがん罹患リスクの差の可能性が示唆された。オッズ比の高い業種の症例については、カルテレビューや病理診断記録の確認などを行ったところ、入手可能であった病歴要約のうち、病理組織学的にがんの診断を確認できたものは 90%近くに達した。

以上、3 年間の研究をとおして、大規模医療データベースから標準化された職業分類と産業分類の双方を用いて、職業と疾病との関連を網羅的に検討する方法が開発された。その方法を ICOD-R に適用した結果、特定の職業や産業は、特定のがん種や循環器疾患の罹患リスクと関連することが示された。本研究で用いた大規模医療データベースである ICOD-R はわが国でも最大級の病職歴データベースである一方、教育歴や収入などの職業以外の社会経済的要因、生活習慣や特殊健康診断の項目に欠損値が少なくないことなど限界があることも明らかになった。北欧諸国では、国勢調査・住民登録とがん登録をリンケージしたデータベース（NOCCA）が整備されており、職業・職種によるがんの超過発生、超過死亡に即応した精度の高い研究を可能としている。わが国においても、同様のデータベースの可能性について検討する必要があると考えられた。

平成 29（2017）年度
（研究分担者）
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A. 研究目的

近年、わが国では、化学工業製造従事者におけるオルト・トルイジンによる膀胱がんや、印刷業者における 1.2.ジクロロプロパンによる胆管がんなど、今まで知られていなかった化学物質の有害性による職業性がんの発症が認められた。しかし、現在のところ、「どのような業種・職種でどのような疾病や死因が多いか」など、幅広い業種・職種を網羅的に探索し状況を把握する手法が開発されていない。そこで、本研究では、既存の大規模医療データ等を用いて、職業ごとのがん及びその他の疾病の過剰リスクに関わる網羅的なサーベイランス手法を開発し、それをもとに特定の化学物質曝露との関連が疑われる疾病の同定や予後の解析につなげていくことを目的とする。

研究期間をとおして、職業・産業とがん、その他の疾病との関連を網羅的に分析する大規模医療データベースとして、主に独立行政法人労働者健康安全機構の入院患者病職歴調査データ（Inpatient Clinico-Occupational Database of Rosai Hospital Group, ICOD-R）を用いた。ICOD-R の詳細は、同機構のホームページに記されている（https://www.research.johas.go.jp/bs/）。また、必要に応じて他のデータベース、地域のがん登録データベースなども利用した。

平成 29 年度の主な研究として腎細胞がんに焦点をあてた。腎細胞がんは、日本では全がんの死亡率の 2%程度であるが、近年は罹患率が増加傾向にある。欧米では、腎細胞がんのハイリスク職業として、化学工業生産工程従事者、機械整備・修理従事者、ドライクリーニング、理容師・美容師が知られていることから取り上げた。また、研究分担者や研究協力者らとともに、幅広い業種・職種を対象にして種々のがん種の罹患状況や予後について網羅的、探索的な検討を行った。さらに、有害物質曝露と関連がしばしば指摘される尿路系腫瘍について、病因論検討を合わせて行った。

平成 30 年度は、ICOD-R を用いて、幅広い職業・産業から、現在、化学物質を扱っているかどうかを同定し、化学物質への曝露と

がん発症のリスクの関連があるかどうかを、がん全体および尿路上皮がん、胆管がんで評価した。つぎに、前年度の研究で用いた職業・産業グループ分類を用いて、職業と各種がん発症のリスクの関連を網羅的に解析した。さらに、わが国の一般環境における化学物質の曝露と関連すると考えられるPRTR（Pollutant Release and Transfer Register：化学物質排出移動量届出制度）制度に基づく排出量・移動量の都道府県別の経年集計と、悪性新生物の主な部位別にみた都道府県別の標準化死亡比（standardized mortality ratio：SMR）の算出を行った。

令和元年度は、がんに次ぐ死因第 2 位である循環器疾患を取り上げ、職業と循環器疾患発症のリスクの関連について網羅的な解析を実施した。また、比較参考例として、海外の病職歴データベースについて文献調査を行った。分担研究においては、ICOD-R の一部対象者についてカルテ（診療録）レビューや病理診断記録の確認などを行うとともに、有害物質曝露による発がんの病因論検討を行った。

B. 研究方法

（平成 29 年度）

データセッティング

独立行政法人労働者健康安全機構が保有する約 650 万件（研究開始時点）の入院患者病職歴調査データを用いて hospital-based case-control study を実施した。入院患者病職歴調査データとは、全国 34 箇所の労災病院に入院した全入院患者の病歴および職業歴を抽出したデータであり、独立行政法人労働者健康安全機構が中央情報センターとして、1984 年からデータベース化を行っている。このデータベースには、各患者の性・年齢等の基本的背景、退院時の主病名、並存疾患名の他に、喫煙、飲酒の生活習慣行動が保有されている。また、2002 年からは病理診断、2005 年からは健康診断で指摘されている生活習慣病（高血圧、糖尿病、肥満等）の情報も保有されている。職業歴については、日本標準職業分類 JSOC および日本標準産業分類 JSIC を用いて、現職から過去 3 つまでの職業分類がコーディングされている。これらの職業分類は、世界標準職業分類および世界標準産業分類と対応している。患者からのデータ取得およびデータベースへのデータ登録は訓練を受けた専門の臨床情報士、看護師等が実施し、患者からインフォームドコンセントを取得している。ICOD-R の使用については、研究者らと独立行政法人労働者健康安全機構との取り決めに基づき、匿名化されたデータセットを取得した。

症例 case と対照 control

解析対象者は 20 歳以上で、1984 年 4 月から 2016 年 3 月に労災病院グループに入院した 71,734 名で、腎細胞がん 3,316 名（上部尿路上皮がん、およびがん既往歴があるものは除く）と対照群として設定した 168,418 名の良性疾患患者である。全国がん登録を参照とすると、この期間に日本で発症した腎細胞がんの 0.8％に相当する。対照群の良性疾患は国際疾病分類（International Classification of Diseases、ICD）に基づき、整形外科疾患（ICD-9, 410-739; ICD-10, M00-M99; 89%）と皮膚科疾患（ICD-9, 680-709; ICD-10, L00-L99; 11%）とした（Prakash 2017）。

職業分類

取得した入院患者病職歴調査データでは、現職から過去 3 つまでの職業が、JSOC および JSIC の 3 桁コードで分類されていたため、最長の職業を用いて各患者を層別化した。抽出された最長職業の種類は莫大な数となるため、4 つの基本的な職業地位、「ブルーカラー職」、「サービス職」、「専門職」、「管理職」に分類した。また、さらにこの職業地位を 3 つの産業別、「ブルーカラー」、「サービス」、「ホワイトカラー」に分けた（H29_図 1）。主婦、学生、無職等の雇用されていない者は解析から除外した。また、女性のホワイトカラー産業の「管理職」については、人数が非常に少なく、腎細胞がんの case を認めなかったため、解析から除外した。また、欧米で知られている腎細胞がんのハイリスク職業（化学工業生産工程従事者、機械整備・修理従事者、ドライクリーニング、理容師・美容師）については、解析の過程でリスク増加を認めなかったため、新たにグループ分けは行わなかった。

共変量

交絡調整のため年齢と入院日（年）を共変量とした。診断や治療の変化を考慮するために、入院日（年）を調整した。職業地位と腎細胞がんの関連の中間媒介変数として、喫煙（pack-year）、飲酒（1 日飲酒量、エタノール g/day 換算）、高血圧、糖尿病、肥満を解析モデルに組み込んだ。

統計解析

解析対象者のうち 11％は、職業、喫煙、飲酒の情報いずれかが欠損しており、20％は職業、喫煙、飲酒の情報いずれも欠損していた。データ欠損群とデータ完全群では患者背景が統計学的に異なっていたため、データ欠損群を除外して解析することはデータ解釈にバイアスを生じる可能性があった。よって、解析対象者 171,734 名の全データを利用して multiple imputation by chain method（MICE）法による多重補完 multiple imputation を実施し、数学的に欠損値を予測し代入した。職業（n = 20,359, 12%）、喫煙（n = 23,692, 14%）、飲酒（n = 48,608, 28%）の欠損値が代入された。Multiple imputation によって作成された 5 個のデータセットを用いた unconditional logistic regression により、ブルーカラー産業のブルーカラー職に対する各職業の腎細胞がんのオッズ比（odds ratio, OR）および 95% 信頼区間（95% confidence interval, 95%CI）を算出した。すべての解析は男女別でおこなった。第一に、年齢と入院日（年）を調整した OR（95％CI）を求めた（H29_モデル 1）。次に喫煙を調整した OR（95％CI）を求めた（H29_モデル 2）。さらに飲酒を調整した OR（95％CI）を求めた（H29_モデル 3）。

高血圧、糖尿病、肥満が職業と腎細胞がんの関連にどのように関与するかは、これらのデータが 2005 年以降しか取得可能でなかったため、2005 年以降に入院した 63,704 名（1,544 名の case、62,160 名の control）を対象に、以下の欠損値を多重補完し解析した：職業（n = 6,943, 11%）、喫煙（n = 6,968, 11%）、飲酒（n = 19,198, 30%）、高血圧（n = 8,507, 13%）、糖尿病（n = 8,508, 13%）、肥満（n = 8,508, 13%）。このサブグループ解析では、高血圧の関与をまず評価し、最終的に高血圧、糖尿病、肥満、年齢、入院日（年）、喫煙、飲酒の全てを調整して、各職業の腎細胞がんの OR（95％CI）を求めた。入院患者を対照群として用いることで選択バイアスが生じる可能性があるため、(1) 全ての良性

疾患の対照群（3,316 名の case と 1,298,207 名の control)と、(2)整形外科疾患患者のみの対照群（3,316 名の case と 150,210 名の control)を用いた 2 種類の感度分析を追加した。さらに、完全データ群による complete case analysis（2,496 名の case と 116,139 名の整形外科疾患 control 群)も実施した。統計学的有意水準は両側 5％とし、STATA/MP13.1（Stata‐Corp LP, College Station, Texas）を使用して統計解析を行った。

（倫理面への配慮）
本研究は既存のデータの二次利用であり、研究対象者に直接の体験は存在しない。研究実施にあたって、東京大学（No. 3890-3）および関東労災病院（独立行政法人労働者健康福祉機構;2014-38）の倫理審査の承認を得た。

（平成 30 年度）
（研究 1）と（研究 2）のデータセッティング
ICOD-R データを用いて、化学物質を扱う職業とがんと関連、ならびに全職業・産業とがんとの関連について、hospital-based case-control study を実施した。ICOD-R の概要、ならびに職業・産業分類については前述のとおりである。平成 30 年度は、ICOD-R 内の特殊健診診断（有機溶剤健康診断、鉛健康診断、特定化学物質健康診断）を受けたか否かの項目を解析に使用した。

（研究 1）化学物質を扱う職業とがん発症のリスクの関連
解析対象者は 20 歳以上で、2005 年 4 月から 2016 年 3 月に労災病院グループに入院した 60,677 名で、全がん 22,951 名（うち尿路上皮がん[腎盂・尿管・膀胱がん]848 名および胆道がん[胆のう・肝外胆道がん]254 名）と 37,726 名の良性疾患患者。Control の良性疾患患者は、国際疾病分類（International Classification of Diseases 10th Revision、ICD-10）に基づき、眼科および耳鼻科疾患（H00-M95, 30.1%）、泌尿器科領域疾患（N00-N99, 39.4%）、感染症疾患（A00-B99, 20.2%）と皮膚科疾患（L00-L99, 10.3%）とした。これらの control 疾患は、発症リスクに職業格差が見られていないため、本研究の趣旨である職業関連の化学物質曝露とがん発症リスクの関連の研究には適していると考えられた。

（研究 2）全職業・産業とがん発症リスクの関係の網羅的評価
解析対象者は 20 歳以上の男性のうち、1984 年 4 月から 2016 年 3 月に労災病院グループに入院した 1,240,370 名で、全がん 214,123 名と 1,026,247 名の良性疾患患者。各 case に対して、性、年齢（5 歳階級）、病院、入院年が等しい control を 5 名、無作為に抽出した。特に注目するがんの部位は、全がんおよび日本人男性の罹患率のトップ 10 位である胃がん、肺がん、大腸がん、前立腺がん、肝臓がん、食道がん、膵臓がん、膀胱がん、腎臓がん（腎盂尿管含む）、悪性リンパ腫とした。Control の良性疾患は、眼科および耳鼻科疾患（ICD-9, 360-389; ICD-10, H00-H95; 36.5%）、泌尿器科領域疾患（ICD-9, 580-629; ICD-10, N00-N99; 42.9%）、感染症疾患（ICD-9, 1-136; ICD-10, A00-B99; 13.6%）と皮膚科疾患（ICD-9, 680-709; ICD-10, L00-L99; 7.0%）とした。

説明変数
研究 1 の化学物質への曝露としては、現在

の職業において、有機溶剤健康診断の実施の有無、鉛健康診断の実施の有無を用いて評価した。それぞれの特殊健診受診者を、それぞれ曝露ありと定義した。特定化学物質健康診断の受診者については、今回のデータセットではがん患者がいなかったため、有機溶剤と鉛についての特殊健診のみの評価とした。

研究 2 の網羅的な職業分類については、現職から過去 3 つまでの職業が、JSOC および JSIC の 3 桁コードで分類されているため、最長の職業を用いて各患者を層別化した。抽出されたおよそ1万種類の最長職業を、先行研究に基づき 4 つの職業(ブルーカラー職、サービス職、専門職、管理職」に分類した。さらに、この職業を 3 つの産業(ブルーカラー産業、サービス産業、ホワイトカラー産業」に分けた(H30_図 1)。また、学生、無職、退職者等の非雇用者は、「その他」のグループとした。

共変量

研究 1 では、交絡調整のため、性、年齢、入院年を共変量とした。診断や治療の変化を考慮するために、入院年を調整した。研究 2 では、職業とがん発症リスクの関連の中間媒介変数として、喫煙(対数変換 pack-year)、飲酒(対数変換 1 日飲酒量、エタノール g/day 換算)を解析モデルに組み込んだ。

統計解析

研究 1 では、欠損値を含まない complete case analysis を実施した。群間比較はカイ2乗検定を行なった。また、化学物質非曝露群に対する化学物質曝露群のオッズ比(odds ratio, OR)および 95%信頼区間(confidence interval, CI)を、性、年齢、入院年を調整して算出した。研究 2 では、解析対象者のうち、1/3 は職業、喫煙、飲酒の情報いずれかが欠損していた。データ欠損群を除外して解析することはデータ解釈にバイアスを生じる可能性があるため、解析対象者 1,240,370 名の全データを利用して Multiple Imputation by Chain Method(MICE)法による多重補完 multiple imputation を実施した。職業(n = 350,751, 28.3%)、喫煙(n = 385,511, 31.1%)、飲酒(n = 478,059, 38.5%)の欠損値に、予測値が代入された 5 個のデータセットを作成した。このデータセットを用いて、各職業のがんのオッズ比を算出した。ブルーカラー産業のブルーカラー職を reference とし、5 つのデータセットで算出された OR と 95%CI は、1 つの OR と 95%CI にプールされた。メインの統計解析モデルは、年齢、病院、入院年をマッチさせた条件付きロジスティック回帰分析を用いた(H30_モデル 1)。次に追加で喫煙と飲酒を調整した OR(95%CI)も求めた(H30_モデル 2)。統計学的有意水準は両側 0.05 %とし、STATA/MP13.1 (Stata‐Corp LP, College Station, Texas)を使用して統計解析を行った。

(倫理面への配慮)

本研究は既存データの二次利用であり、研究対象者に対する直接の体験や侵襲はない。研究実施については、東京大学(No. 3890-5)および関東労災病院(独立行政法人労働者健康福祉機構;2014-38)の倫理審査の承認を得て実施された。

(研究 3)都道府県別の PRTR と悪性新生物の標準化死亡比(SMR)の算出

PRTR データについては、PRTR 制度に基づき届出された排出量・移動量の集計結果

（http://www.meti.go.jp/policy/chemical_management/law/prtr/6.html）より、全国および都道府県別の排出・届出先別の集計値をCSV形式で収集した。対象年度は PRTR の届出が開始された 2001（平成 13）年度からデータ収集時（最終日：2019 年 1 月 23 日）までに公表されていた 2016（平成 28）年度までとした。

悪性新生物による都道府県別 SMR については、2007（平成 19）年から 2015（平成 27）年までの性別・年齢（5 歳階級）別人口および悪性新生物（死因簡単分類コード 02100～02121）による性別・年齢（5 歳階級）別死亡数を、全国および都道府県別に収集した。

分析方法として、PRTR データについては、2016 年度に届出された排出量・移動量の合計（全国）上位 10 物質を分析対象物質とした。当該 10 物質の全国および都道府県別の排出量（kg / 年）と排出・移動量の合計（kg / 年）をデータとし、単位を t / 年 に換算した。排出・移動量の合計（t / 年）と排出量（t / 年）の差から、移動量（t / 年）を算出して用い、物質ごとに、2001 年度から 2016 年度までの全国排出量・移動量の推移と 2016 年度の都道府県別排出量・移動量をグラフに示した。「鉛およびその化合物」（排出量・移動量の合計の順位：9 位）は 2008 年度の政令改正前の物質名称（物質番号：230）である。政令改正により届出対象物質の見直しが行われており、対応する改正後の物質は「鉛（物質番号：304）」と「鉛化合物（物x番号：305）」であるため、これらの量を合計して用いた。

SMR については、2007 年から 2015 年までの悪性新生物の部位別 SMR（性別）を都道府県別に算出した。都道府県別 SMR は年によりばらつきがあるため、直近 5 年間（2011 年から 2015 年）の平均 SMR を算出して用いた。悪性新生物の主な部位として悪性新生物（死因簡単分類コード 2100）、食道（2102）、胃（2103）、結腸（2104）、直腸 S 状結腸移行部及び直腸（2105）、肝及び管内胆管（2106）、胆のう及びその他の胆道（2107）、気管，気管支及び肺（2110）、乳房（2112）、子宮（2113；女性のみ）、前立腺（2115；男性のみ）、膀胱（2116）、白血病（2116）の 13 部位を選択した。

両者を図示し、関連があるかを検討した。

（令和元年度）

データセッティング

ICOD-R データを用いて、職業・産業と循環器疾患の関連について、hospital-based case-control study を実施した。ICOD-R の概要、ならびに職業・産業分類については前述のとおりである。職業等は、ICOD-R に記された職業等のうち、最長職業を用いた。

症例 case と対照 control

解析対象者は 20 歳以上で、1984 年 4 月から 2016 年 3 月に労災病院グループに入院した 1,128,591 名（全循環器疾患患者 128,615 名と 999,976 名の良性疾患患者）である。各 case に対して、性、年齢（5 歳階級）、病院、 入院年が等しい control を最大 10 名、無作為にマッチングして抽出する方式をとった。しかし、マッチングの過程で、必ずしも各 case に対して control が 10 名に到達しなかった（平均の control 数は 8 [range 1¬‑10]、10 名の control が得られたマッチング例は全体の 54.9%）。Control 症例のうち、循環器疾患として入院した症例は control 群からは除いた。

循環器疾患の分類としては、全循環器疾

患（ICD-9, 390‐459; ICD-10, I00‐99）、狭心症（ICD-9, 413; ICD-10, I20）、急性心筋梗塞（ICD-9, 410; ICD-10, I21）、両者で構築される冠動脈疾患、ならびに、いわゆる脳卒中（くも膜下出血、脳内出血、脳梗塞）を取り上げた。詳細をR1_表 1 に示す。

Control 群は、眼科および耳鼻科疾患（ICD-9, 360-389; ICD-10, H00-H95; 31.1%）、泌尿器科領域疾患（ICD-9, 580-629; ICD-10, N00-N99; 31.1%）、感染症疾患（ICD-9, 1-136; ICD-10, A00-B99; 10.7%）、皮膚科疾患（ICD-9, 680-709; ICD-10, L00-L99; 5.9%）、症状・徴候・異常臨床所見（ICD-9, 780-799; ICD-10, R00-R99; 7.3%）、先天的疾患などのその他の疾患 (ICD-9, 280-289, 740-779; ICD-10, D50-D77, P00-P96, Q00-Q99; 13.9%)とした。循環器疾患の既往がある症例や初回入院でない症例は control 群から除外した。

共変量

交絡調整のため性、年齢、病院、入院年をマッチングにより調整した。診断や治療の変化、生活習慣（例えば食塩摂取量）を考慮するために、入院年と病院（地域の代替変数）をマッチングにより調整した。職業と循環器疾患発症リスクの関連の中間媒介変数として、喫煙（対数変換 pack-year）、飲酒（対数変換 1 日飲酒量、エタノール g/day 換算）を解析モデルに組み込んだ。

統計解析

解析対象者のうち、合わせて 20%について、職業、喫煙、飲酒の情報いずれかが欠損していた。具体的には、職業 6.0%、喫煙 9.5%、飲酒 18.6%であった。データ欠損群を除外して解析することはデータ解釈にバイアスを生じる可能性があるため（R1_表 2）、解析対象者 1,128,591 名の全データを利用して Multiple Imputation by Chain Method（MICE）法による多重補完 multiple imputation を実施し、数学的に欠損値を予測し代入したデータセットを 5 セット作成し統合して解析した。この統合したデータセットを用いて、各職業の循環器疾患のオッズ比（OR）と 95%信頼区間（CI）を算出した。Reference はブルーカラー産業のブルーカラー職とした。メインの統計解析モデルは、年齢、病院、入院施設、入院年をマッチさせた条件付きロジスティック回帰分析を用いた（R1_モデル 1）。次に、喫煙と飲酒を調整したオッズも求めた（R1_モデル 2）。統計学的有意水準は両側 0.05%とした。統計解析には、STATA/MP13.1（StataCorp LP, College Station, Texas）を使用した。

海外の病職歴データベース

職歴と疾病の関連についての先行研究から、Nordic Occupational Cancer (NOCCA) project について、データベースの詳細について文献調査を行った。

（倫理面への配慮）

病職歴データや試料を用いた研究については、東京大学（No. 3890-5）および関東労災病院（2014-38）の倫理審査の承認を得て実施された。

C. 研究結果

（平成 29 年度）

男性においては、ブルーカラー産業のブルーカラー職従事者と比べると、全ての産業で職業地位の高い人（専門職や管理職）で腎細胞がんのリスクが高かった（H29_図 2）。職

業地位が一番高い管理職従事者については、minimally adjusted OR（H29_モデル 1）は 1.47（ホワイトカラー産業）から 1.62（ブルーカラー産業）の範囲で分布し（H29_表 1）、これらの OR は喫煙、飲酒を調整した後でも有意に腎細胞がんのリスクと関連していた（fully adjusted OR（H29_モデル 3）は 1.48（ホワイトカラー産業）から1.61（ブルーカラー産業）の範囲に分布していた）。女性においては、有意ではないものの、管理職と腎細胞がんのリスクの関連の傾向がサービス産業で見られ（H29_図 2）、minimally adjusted OR（H29_モデル 1）と fully adjusted OR（H29_モデル 3）の効果のサイズは同様であった。

サブグループ解析においては、男性では、高血圧、糖尿病、肥満がそれぞれ独立した腎細胞がんのリスク因子であった（高血圧 OR＝1.36、95% CI 1.20−1.54)。職業地位の高い人と関連する腎細胞がんのリスクは、高血圧や喫煙等の全ての交絡および中間媒介因子を調整することにより大きく減少したものの、専門職においてはブルーカラー産業（OR＝1.37、95% CI 1.06−1.78）とホワイトカラー産業（OR＝1.26、95% CI 1.00−1.59）では、腎細胞がんのリスクと関連が持続した。女性については、有意ではないものの、サービス産業で職業地位の高い人と関連する腎細胞がんのリスクの関連の傾向が見られた。感度分析でも同様のパターンを示した。また、本データベースの職業地位の分布は、日本の一般人口における職業地位の分布と同様であり、最長職業の平均期間は 20 年以上であった。

（平成 30 年度）

（研究 1）化学物質を扱う職業とがん発症のリスクの関連

全がん case 例のうち有機溶剤健康診断受診者は 986/21,965 例（4.3%）であり、control 例のうち有機溶剤健康診断受診者は 1,673/37,726 例（4.4%）で、分布に統計学的な有意差を認めなかった（P=0.42）。全がん case 例のうち鉛健康診断受診者は 44/22,951 例（0.2%）であり、control 例のうち鉛健康診断受診者は 87/37,726 例（0.2%）で、分布に統計学的な有意差を認めなかった（P=0.32）。全がんについての調整済みオッズ比はそれぞれ、OR 有機溶剤=1.01 (95% CI 0.92‐1.10)および OR 鉛=0.95 (95% CI 0.65‐1.40)であり、曝露によるがん全体の発生率の差は検出できなかった。有機溶剤特殊健診受診者について、尿路上皮がんに特異的な調整済みオッズ比は OR 有機溶剤=0.88 (95% CI 0.65‐1.19)であり、胆道がんでは OR 有機溶剤=0.77 (95% CI 0.41‐1.47)であり、既報の化学物資曝露による発がんから懸念される発生率の差は検出できなかった。

（研究 2）各職業とがん発症リスクの関係の網羅的評価

ブルーカラー産業のブルーカラー職従事者と比べると、専門職や管理職従事者で胃がんおよび肺がんのオッズが低かった（H30_表 1）。これらのオッズ比は、喫煙、飲酒を調整した後でも有意に職業と関連していた。胃がんの最大調整済み OR は、ホワイトカラー産業の管理職の 0.80 からブルーカラー産業の専門職の 0.93 の範囲に分布し、肺がんの最大調整済み OR は、ホワイトカラー産業の管理職の 0.66 からブルーカラー産業の管理職の 0.83 の範囲に分布した（H30_モデル 2、H30_表 1)。残りの頻度の高いがんのうち、肝臓がん、食道がん、膀胱がんおよび悪性

リンパ腫で、ホワイトカラー産業の管理職でオッズが低く、膵臓がんでも同様の傾向が見られたが、大腸がんでは職業間での差は検出できなかった（H30_表 1）。一方で、前立腺がんおよび腎がんでは専門職や管理職従事者でオッズが高い傾向がみられた（H30_表 1）。がん全体としては、専門職や管理職従事者でオッズがやや低い傾向が見られた（H30_表 1）。女性については、男性と同様な傾向が胃・肺がんで見られた。

（研究 3）都道府県別の PRTR データと悪性新生物 SMR

2016 年度に届出された排出量・移動量の合計（全国）上位 10 物質は、トルエン、マンガン及びその化合物、キシレン、クロム及び三価クロム化合物、エチルベンゼン、ふっ化水素及びその水溶性塩、ジクロロメタン（塩化メチレン）、N, N-ジメチルホルムアミド、鉛及びその化合物、ほう素及びその化合物であった。これら 10 物質について、2001 年度から 2016 年度までの 16 年間の状況、ならびに 2016 年度の都道府県別の状況を図示した（資料 1）。物質ごとの排出量・移動量は都道府県によって大きく異なり、また、経年変化にも特徴があった。都道府県別の悪性新生物の 5 年平均 SMR については、がん種によって都道府県で異なる傾向がみられた（資料 2）。

（令和元年度）

ブルーカラー産業のブルーカラー職従事者（reference）と比べると、専門職や管理職従事者で冠動脈疾患のオッズが高かった（R1_表 3）。これらのオッズ比は、喫煙、飲酒を調整した後でも有意に関連していた（R1_図 1）。循環器疾患の最大の OR は、サービス産業の管理職で観察された：OR 1.19（95% CI 1.08-1.31, R1_モデル 2)。ブルーカラー/ホワイトカラー産業の専門職/管理職では、狭心症のオッズは高かったが、急性心筋梗塞のオッズは null の方向にシフトしていた（R1_図 2、R1_表 3）。しかし、サービス産業の専門職/管理職では、狭心症も急性心筋梗塞のオッズも高いままであった（R1_図 2、R1_表 3）。

一方で、ブルーカラー産業のブルーカラー職従事者（reference）と比べると、専門職や管理職従事者で脳卒中のオッズは低かった（R1_図 1、R1_表 3）。この protective な職業と脳卒中の関連は、ブルーカラー産業で働く専門職の OR 0.77 からブルーカラー産業で働く管理職の OR 0.88 の範囲で観察された（R1_モデル 2）。この protective な職業と脳卒中の関連は、くも膜下出血、脳内出血、脳梗塞の各種疾患でも観察された（R1_図 2）。

結果的に、専門職/管理職はごく僅かであるが循環器疾患全体のリスクが低くなる傾向にあった（R1_表 3）。つまり、専門職や管理職従事者で上昇する心血管疾患のリスクが、脳血管疾患のリスクが下がることにより相殺されていることが示唆された。

海外の病職歴データベース

Nordic Occupational Cancer (NOCCA) project は、1943 年にデンマークで開始された全国がん登録に発する。その後、1953 年にフィンランドとノルウェー、1955 年にアイスランド、1958 年にスウェーデンで全国がん登録が開始された。さらに、スウェーデンにおいて、国勢調査（1960 年実施）とがん登録の個人ベースのリンケージが最初に行われ、その後、各国が追随した。職業分類も 5 カ国

間で標準化が行われた（Pukkala E, et al, 2009）。最近では、従来型の数年毎実施の国勢調査を廃止し、社会保障番号や現職などと紐付けされ電子化された住民登録データ（computerised central population registries）とのリンケージを行っている国もある。同プロジェクトによれば、男女のがんの約 5%が仕事（職業）と関連し、男性のがんの約 35%、女性のがんの約 16%が社会経済階層と関連しているとされる（Pukkala E, 2015）。職業・産業による種々のがんの標準化罹患比（standardised incidence ratios）を推定している（資料 3）（Pukkala E, et al, 2009）。また、日本の印刷業者における 1.2.ジクロロプロパンによる胆管がん発生の報告に対応して、印刷業従事者に関して NOCCA データベースを用いた後ろ向きコホート研究が実施されている（Vlaanderen J, et al, 2013）。

D. 考察

（平成 29 年度）

本年度の研究により、職業地位と腎細胞がんのリスクの関連が初めて示された。すなわち、男性において、職業地位が高い人の方が腎細胞がんのリスクが高いことが示された。また、日本においては、高血圧が腎細胞がんの独立したリスクファクターであることを初めて明らかにし、高血圧、糖尿病、肥満等のストレス関連因子を通じて、職業地位の高い人の腎細胞がんのリスクが上昇する経路が示唆された。これらの結果は職業ストレスと腎細胞がんとの関連の可能性を示唆している。なお、本研究は、日本で行われた腎細胞がんと職業リスクに関わる最大規模の研究の1つであるが、それでも日本全体で発症した腎細胞がんの 1%未満しか捉えておらず、本研究の一般化可能性については限定的であるといえる。

本研究の強みは、大規模なサンプルサイズのおかげで、解析対象者の職業背景を、標準化された職業分類と産業分類の双方を用いて、網羅的に分類する手法を開発できた点があげられる。日本における労働人口の転職の割合は、欧米と比較して低く、本研究でも最長職業の平均期間が 20 年以上と長かったため、コホート研究等で用いられる観察開始時点の職業よりは、生涯を通じての職業地位の影響をより捉えている可能性が高い点も強みである。

（平成 30 年度）

本年度の研究で実施した特殊健康診断を化学物質曝露の代理指標とした分析では、化学物質曝露とがんの罹患リスク上昇との関連は見られなかった。他方、化学物質の曝露とは直接の関係はないが、わが国の男性のがんにおいて、職業と各がん罹患のリスクの間に一定の関連のあることを初めて明らかした。特に専門職や管理職従事者に注目することで、日本人で頻度の高い胃がん、肺がん、肝臓がん、食道がん、膀胱がんおよび悪性リンパ腫において、専門職や管理職従事者の罹患リスクの低いことを明らかにした。分担研究者らの報告では、特定の産業分野従事者でがん罹患の高い可能性が示唆されている。今後、産業ならびに職業（職種・職階）による化学物質曝露の違い、さらに職業による生活習慣の違いなどを詳細に検討し、それらをもとに分析を進めることによってがん罹患リスクに係わる要因を網羅的に明らかにする手がかりを得ることができると考えられる。

本研究の強みは、大規模なサンプルサイズを用いて、日本における職業とがん罹患リ

スクの関連を、標準化された職業分類と産業分類の双方を用いて網羅的に評価し、各がんにおいて個別に職業との関連を明らかにした点があげられる。また、診断がカルテ情報から直接抽出されていることから、レセプト等の研究と比べて誤分類が少ない点が挙げられる。また、最長の職業を抽出した点も、死亡統計等を用いた先行研究と比べて、職業従事情報としての精度が高い。本研究の限界は、まず、hospital-based case-control 研究という研究デザイン上、コントロール群の選び方による選択バイアスが生じている可能性がある点である。しかし、準備段階として行った感度分析では、コントロール群を変更して得られた結果も同じであった。ICOD-R データの職業背景は日本の政府統計における職業分布と同様であるから、代表性はある程度担保されていると考えられる。また、欠損値の存在が結果に影響を与える可能性があったが、multiple imputation と感度分析の complete case analysis のいずれの手法でも結果は同様であったことから、結果に大きな影響は与えていないと考えられる。なお、肥満や食事、身体活動などについては評価ができていないため、今後の研究課題である。

PRTR データ（資料 1）や悪性新生物 SMR（資料 2）について、都道府県ごとの特徴がみられた。PRTR データの排出量と環境検出量を比較した先行研究によれば、届出排出量が多い物質については、排出量と環境中の検出量との整合性が高く、排出状況が検出状況を概ね反映していることが示されている（岡田泰史、ほか．2004）。したがって、PRTR データは一般環境からの化学物質曝露の指標になりうると考えられる。今回、都道府県別の PRTR データと悪性新生物 SMR の間に明らかな関連をみつけることはできなかった。

（令和元年度）

本研究は、特に専門職や管理職従事者に注目することで、職業と循環器疾患の罹患リスクの関連を示すことができた。特筆すべきは、日本の専門職/管理職で心血管疾患の罹患リスクが高くなることが示され、この傾向は現在の欧米諸国の傾向と反対であった。さらに、同じ集団において職業と 2 大循環器疾患―冠動脈疾患と脳卒中―のリスクの関連の向きが異なるという結果を初めて示した研究であり、専門職/管理職従事者で上昇する心血管疾患のリスクが、脳血管疾患のリスクが下がることにより相殺されていることを示唆した。日本は、質の高い循環器疾患の予防と治療戦略を職業に関係なく広く取り組んできているが、その中で、喫煙や飲酒の影響を取り除いても、職業と循環器疾患が関連することを今回の研究は示唆している。

欧米諸国では、循環器疾患のリスクは職業階層のような社会経済的要因と非常に強い結びつきがあり、 社会経済的に有利な人ほど（例えば専門職や管理職従事者）循環器疾患のリスクが低くなるとされる。しかし、この循環器疾患の罹患リスクの「勾配」は、歴史上不変であったわけではない。20 世紀前半には、冠動脈疾患は「executive coronary」という用語で描写されるように、豊かさによる疾患として認識されていた。しかし 20 世紀の間にはこの勾配は逆転した。 これは、冠動脈疾患のリスクに対する理解が浸透したこと（禁煙、定期的な運動、食事、 高血圧や脂質異常症の治療など）、および社会経済的に有利な人ほど健康的な生活習慣をより迅速に取り入れたことを反映している。今回の

我々の報告は、この歴史的なリスクの推移には必ずしも一致しない。欧米諸国の趨勢に照らし合わせれば、日本の喫煙率や適量以上の飲酒率は、専門職/管理職でも依然として高い。また、本研究では、喫煙や飲酒によって循環器疾患の罹患リスクの職業による差を完全には説明できなかったことから、喫煙や飲酒以外の生活習慣、例えば不十分な身体活動量、高血圧、糖尿病、肥満などの関与が考えられるが、これらの情報は本研究で用いたデータベースでは十分に確認することができなかった。今後の課題である。

本研究にはいくつか限界がある。第一に hospital-based case-control 研究のデザイン上、コントロールの選択バイアスが生じている可能性がある。マッチングの過程で全ての case について 10 例の control が得られなかったことも、バイアスを生じると考えられる。しかし、感度分析ではコントロール群を変更して得られた結果は同様であった。また、ICOD-R データの職業背景は日本の政府統計における職業分布と同様であったことから、代表性は担保されていると考えられる。第二に、教育や収入などの職業以外の代表的な社会経済的要因、入院時の疾患の重症度、循環器疾患の生活習慣リスクファクター（高血圧、糖尿病、肥満、身体活動）が評価できていない。また、職業ストレスや長時間労働などの職業関連リスクファクターも評価できていない。さらに、今回扱った循環器疾患について、労災事例であるか否かが評価できていない。これらの限界はあるものの、本研究の強みは、職業と循環器疾患の罹患リスクの関連について評価した欧米諸国以外の研究の中で、もっとも大規模なサイズの研究であることが挙げられる。さらに、最長職業を用いて評価しているため、職業の誤分類の可能性も低くなっていることが挙げられる。今後は、先に挙げた本研究の限界を踏まえ、生活習慣および職業関連のリスクファクターをさらに広げて調査、収集することにより、観察された職業と循環器疾患の罹患リスクの関連をより精確に解明することを期待したい。

なお、分担研究においては、化学物質曝露機会の多い製造業に限定した詳細な分析から、製造業種内でのがん罹患リスクの差の可能性が示唆されている。また、オッズ比の高い業種の症例については、カルテレビューや病理診断記録の確認などを行った。入手可能であった病歴要約のうち、病理組織学的に癌の診断を確認できたものは 90%近くに達し、ICOD-R が精度の高いデータベースであることが確認された。

北欧諸国では、がん登録と国勢調査・住民登録を個人レベルでリンケージしたデータベース（NOCCA）が整備され、職業・職種によるがんの超過発生、超過死亡に即応した研究が可能な体制が構築されている。今後、法制度の整備も含めて、我が国での可能性について検討する必要があると考えられる。

E. 結論

3 年間の研究をとおして、大規模医療データベースから標準化された職業分類と産業分類の双方を用いて、職業と疾病との関連を網羅的に検討する方法が開発された。その方法を ICOD-R に適用した結果、特定の職業や産業は、特定のがん種や循環器疾患の罹患リスクと関連することが示された。本研究で用いた大規模医療データベースである ICOD-R はわが国でも最大級の病職歴データベースである一方、教育歴や収入などの職業以外の社会経済的要因、生活習慣や特殊健康診断の項目に欠損値が少なくない

ことなど限界があることも明らかになった。北欧諸国では、国勢調査・住民登録とがん登録をリンケージしたデータベース（NOCCA）が整備されており、職業・職種によるがんの超過発生、超過死亡に即応した精度の高い研究を可能としている。わが国においても、同様のデータベースの可能性について検討する必要があると考えられた。

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F. 健康危険情報

なし

G. 研究発表

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H. 知的財産権の出願・登録

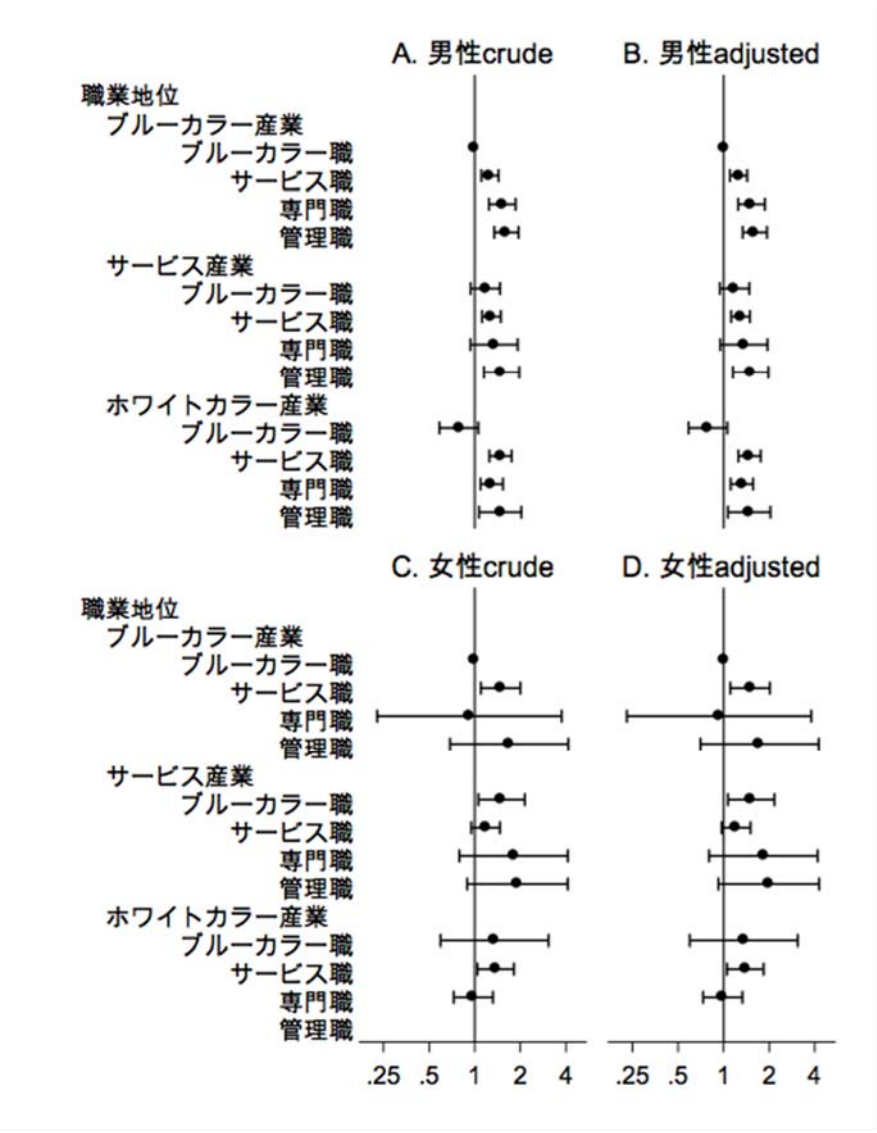
なし

H29_図 1　日本標準職業分類と日本標準産業分類を用いた最長職業による職業地位分類

職業分類	日本標準職業分類	コード
ブルーカラー職	保安職業、農林漁業、生産工程、定置・建設機械運転、建設・採掘、運搬・清掃・包装等従事者	43–59, 64–73
サービス職	事務、販売、サービス職業、輸送・機械運転（鉄道、自動車、船舶・航空機、その他の輸送）従事者	25–42, 60–63
専門職	専門的・技術的職業従事者	05–24
管理職	管理的職業従事者	01–04
産業分類	**日本産業職業分離**	**コード**
ブルーカラー産業†	農林漁業、鉱業・採石業・砂利採取業、建設業、製造業、電気・ガス・熱供給・水道業、運輸業・郵便業	A–F, H
サービス産業	卸売業・小売業、宿泊・飲食サービス業、生活関連サービス業・娯楽業、複合サービス事業、サービス業（他に分類されないもの）	I, M, N, Q, R
ホワイトカラー産業ǂ	情報通信業、金融業，保険業、不動産業，物品賃貸業、学術研究，専門・技術サービス業、医療，福祉、公務（他に分類されるものを除く）	G, J, K, O, P, S

† 廃棄物処理業を含む（Code R88）. ǂ 政治・経済・文化団体（Code R93），鉄道業（Code H42）、道路旅客運送業（Code H43）、航空運輸業（Code H46）を含む.

H29_図 2　男女別の各職業地位・産業別の腎細胞がんのオッズ比。オッズ比（黒丸●）と 95%信頼区間（横線―）は欠損値を多重補完して推計した。（A, C）は年齢と入院年が調整された男性および女性のそれぞれのオッズ比、（B、D）はさらに喫煙と飲酒を追加調整されたオッズ比である。症例数と対照数は、それぞれ 2,703 名と 111,925 名（男性）と 613 名と 56,493 名（女性）である。



H29_表 1　各職業地位・産業別の腎細胞がんのオッズ比

職業地位	対照	症例	オッズ比（95%信頼区間）[a,b]		
			モデル 1	モデル 2	モデル 3
	%	%			
男性					
全数	111,925	2,703			
ブルーカラー産業					
ブルーカラー職	39.0	34.2	1.00	1.00	1.00
サービス職	13.5	14.2	1.26 (1.11–1.44)	1.26 (1.10–1.43)	1.26 (1.10–1.43)
専門職	4.3	5.0	1.52 (1.24–1.86)	1.53 (1.25–1.88)	1.53 (1.25–1.87)
管理職	3.2	5.8	1.62 (1.35–1.95)	1.61 (1.34–1.94)	1.61 (1.34–1.93)
サービス産業					
ブルーカラー職	4.7	4.0	1.17 (0.94–1.47)	1.18 (0.94–1.47)	1.18 (0.94–1.48)
サービス職	13.4	13.2	1.29 (1.12–1.49)	1.29 (1.12–1.49)	1.29 (1.12–1.49)
専門職	1.1	1.2	1.34 (0.94–1.92)	1.36 (0.95–1.95)	1.36 (0.95–1.95)
管理職	1.6	2.7	1.50 (1.15–1.97)	1.51 (1.15–1.97)	1.51 (1.15–1.97)
ホワイトカラー産業					
ブルーカラー職	3.6	2.0	0.78 (0.58–1.05)	0.79 (0.59–1.06)	0.79 (0.59–1.06)
サービス職	8.1	9.6	1.48 (1.25–1.75)	1.48 (1.25–1.76)	1.48 (1.25–1.76)
専門職	6.5	6.5	1.29 (1.09–1.53)	1.32 (1.11–1.56)	1.32 (1.11–1.57)
管理職	1.0	1.7	1.47 (1.07–2.03)	1.48 (1.07–2.04)	1.48 (1.07–2.04)
女性					
全数	56,493	613			
ブルーカラー産業					
ブルーカラー職	28.9	28.1	1.00	1.00	1.00
サービス職	8.8	10.0	1.48 (1.10–2.00)	1.49 (1.10–2.01)	1.49 (1.11–2.02)
専門職	0.5	0.3	0.92 (0.23–3.75)	0.92 (0.23–3.76)	0.93 (0.23–3.79)
管理職	0.5	0.8	1.69 (0.69–4.15)	1.70 (0.69–4.18)	1.73 (0.70–4.25)
サービス産業					
ブルーカラー職	4.5	6.4	1.50 (1.06–2.14)	1.52 (1.07–2.16)	1.52 (1.07–2.17)
サービス職	28.2	28.1	1.18 (0.95–1.47)	1.20 (0.97–1.50)	1.21 (0.97–1.50)
専門職	0.8	1.0	1.81 (0.79–4.12)	1.82 (0.80–4.14)	1.83 (0.80–4.18)
管理職	0.6	1.1	1.91 (0.89–4.11)	1.97 (0.91–4.23)	1.99 (0.92–4.27)
ホワイトカラー産業					
ブルーカラー職	0.9	1.0	1.35 (0.59–3.07)	1.35 (0.59–3.08)	1.36 (0.60–3.09)
サービス職	12.0	12.9	1.37 (1.04–1.81)	1.38 (1.05–1.82)	1.39 (1.05–1.84)

専門職	14.5	10.4	0.98 (0.73–1.32)	0.98 (0.73–1.32)	0.99 (0.73–1.33)
管理職	–	–	–	–	–

[a] 年齢・入院年（交絡因子）を調整した多重補完後ロジスティック回帰（モデル 1）

[b] 喫煙（中間媒介因子、モデル 2）、喫煙および飲酒（中間媒介因子、モデル 3）を追加で調整

H30_表 1　各職業における頻度の高い男性のがんのオッズ比

Characteristics		Control, %[a]	Case, %[a]	オッズ比（95%信頼区間）[b]	
				モデル 1	モデル 2
食道がん		n=30,545	n=6,317		
職業					
ブルーカラー産業	ブルーカラー職	32.4	34.5	1.00	1.00
	サービス職	11.2	11.4	0.96 (0.87–1.06)	0.95 (0.85–1.05)
	専門職	3.3	2.9	0.82 (0.67–0.99)	0.81 (0.66–0.98)
	管理職	4.3	4.6	0.99 (0.85–1.16)	0.95 (0.81–1.11)
サービス産業	ブルーカラー職	3.0	3.1	1.00 (0.83–1.21)	1.03 (0.84–1.24)
	サービス職	10.6	11.2	1.01 (0.91–1.11)	1.02 (0.92–1.13)
	専門職	0.9	1.0	1.04 (0.77–1.40)	1.02 (0.75–1.40)
	管理職	2.2	2.1	0.91 (0.74–1.13)	0.90 (0.72–1.13)
ホワイトカラー産業	ブルーカラー職	1.9	2.0	1.00 (0.81–1.25)	1.03 (0.83–1.27)
	サービス職	6.7	5.9	0.83 (0.71–0.95)	0.82 (0.71–0.95)
	専門職	4.8	4.0	0.78 (0.66–0.93)	0.82 (0.70–0.97)
	管理職	1.4	1.1	0.70 (0.49–0.99)	0.73 (0.52–1.02)
その他		17.3	16.2	0.86 (0.78–0.94)	0.96 (0.87–1.06)
喫煙[c]		2.31	2.86		1.19 (1.16–1.21)
飲酒[d]		2.37	3.02		1.29 (1.26–1.33)
胃がん		n=203,506	n=42,510		
職業					
ブルーカラー産業	ブルーカラー職	32.5	35.3	1.00	1.00
	サービス職	10.8	11.0	0.95 (0.90–0.99)	0.94 (0.90–0.99)
	専門職	3.0	3.0	0.93 (0.87–0.99)	0.93 (0.87–1.00)
	管理職	4.3	4.4	0.95 (0.90–1.02)	0.93 (0.87–0.99)
サービス産業	ブルーカラー職	2.9	3.0	0.94 (0.86–1.01)	0.94 (0.87–1.02)
	サービス職	10.6	10.3	0.91 (0.87–0.95)	0.91 (0.87–0.95)
	専門職	0.9	0.8	0.85 (0.73–0.98)	0.86 (0.74–1.00)
	管理職	2.2	2.0	0.86 (0.79–0.94)	0.86 (0.79–0.94)
ホワイトカラー産業	ブルーカラー職	1.9	1.9	0.92 (0.84–1.01)	0.93 (0.85–1.02)
	サービス職	6.9	6.3	0.84 (0.80–0.89)	0.85 (0.81–0.90)
	専門職	5.0	4.2	0.77 (0.72–0.82)	0.80 (0.75–0.86)
	管理職	1.5	1.3	0.79 (0.71–0.89)	0.80 (0.72–0.90)
その他		17.8	16.5	0.83 (0.80–0.86)	0.86 (0.83–0.89)
喫煙[c]		2.26	2.59		1.12 (1.11–1.13)

飲酒 [d]		2.32	2.53		1.06 (1.05–1.07)
大腸がん		n=128,696	n=27,074		
職業					
ブルーカラー産業	ブルーカラー職	31.6	32.3	1.00	1.00
	サービス職	11.5	11.7	1.01 (0.96–1.07)	1.01 (0.96–1.07)
	専門職	3.4	3.5	1.02 (0.94–1.12)	1.02 (0.94–1.12)
	管理職	4.1	4.0	0.99 (0.92–1.06)	0.97 (0.90–1.04)
サービス産業	ブルーカラー職	3.0	3.2	1.05 (0.97–1.14)	1.07 (0.98–1.15)
	サービス職	11.0	11.4	1.02 (0.96–1.08)	1.02 (0.96–1.08)
	専門職	1.0	0.9	0.91 (0.77–1.09)	0.93 (0.78–1.10)
	管理職	2.0	2.1	1.01 (0.91–1.13)	1.01 (0.90–1.13)
ホワイトカラー産業	ブルーカラー職	1.9	1.8	0.89 (0.77–1.02)	0.89 (0.77–1.02)
	サービス職	7.1	6.9	0.96 (0.89–1.04)	0.97 (0.90–1.04)
	専門職	5.1	5.1	0.96 (0.89–1.04)	0.99 (0.92–1.06)
	管理職	1.4	1.2	0.88 (0.77–0.99)	0.88 (0.78–1.00)
その他		17.0	16.1	0.90 (0.85–0.95)	0.94 (0.89–0.99)
喫煙 [c]		2.38	2.56		1.06 (1.05–1.07)
飲酒 [d]		2.45	2.67		1.09 (1.08–1.10)
肝臓がん		n=88,342	n=18,354		
職業					
ブルーカラー産業	ブルーカラー職	31.9	32.7	1.00	1.00
	サービス職	11.1	11.6	1.02 (0.96–1.08)	1.02 (0.96–1.08)
	専門職	3.1	2.8	0.87 (0.76–0.99)	0.87 (0.76–0.99)
	管理職	4.6	5.1	1.09 (1.00–1.19)	1.07 (0.98–1.17)
サービス産業	ブルーカラー職	2.9	3.1	1.03 (0.93–1.14)	1.04 (0.94–1.15)
	サービス職	10.7	10.6	0.97 (0.91–1.03)	0.97 (0.92–1.03)
	専門職	0.8	0.7	0.89 (0.73–1.09)	0.91 (0.75–1.11)
	管理職	2.1	2.2	1.01 (0.88–1.16)	1.01 (0.88–1.16)
ホワイトカラー産業	ブルーカラー職	1.9	1.7	0.84 (0.74–0.96)	0.84 (0.74–0.96)
	サービス職	7.0	6.0	0.84 (0.77–0.92)	0.85 (0.78–0.93)
	専門職	4.9	3.7	0.74 (0.67–0.81)	0.76 (0.69–0.84)
	管理職	1.6	1.3	0.81 (0.67–0.97)	0.81 (0.68–0.97)
その他		17.3	18.6	1.04 (0.98–1.10)	1.07 (1.00–1.14)
喫煙 [c]		2.28	2.51		1.09 (1.07–1.10)
飲酒 [d]		2.34	2.49		1.04 (1.02–1.05)
膵臓がん		n=23,635	n=4,976		
職業					

ブルーカラー産業	ブルーカラー職	31.9	33.6	1.00	1.00
	サービス職	10.7	11.7	1.04 (0.93–1.16)	1.03 (0.93–1.15)
	専門職	3.1	2.9	0.88 (0.69–1.13)	0.89 (0.70–1.13)
	管理職	4.4	4.4	0.96 (0.80–1.16)	0.95 (0.79–1.14)
サービス産業	ブルーカラー職	3.1	3.2	0.99 (0.80–1.22)	1.01 (0.82–1.24)
	サービス職	10.5	10.2	0.92 (0.77–1.11)	0.93 (0.77–1.12)
	専門職	0.9	0.9	0.92 (0.62–1.39)	0.93 (0.62–1.40)
	管理職	2.1	2.2	1.00 (0.79–1.27)	1.00 (0.79–1.27)
ホワイトカラー産業	ブルーカラー職	2.0	1.6	0.75 (0.58–0.98)	0.76 (0.58–0.99)
	サービス職	6.7	5.9	0.83 (0.72–0.96)	0.84 (0.73–0.96)
	専門職	4.8	4.5	0.90 (0.75–1.07)	0.93 (0.78–1.11)
	管理職	1.5	1.3	0.83 (0.62–1.11)	0.85 (0.63–1.14)
その他		18.2	17.6	0.88 (0.80–0.97)	0.91 (0.83–1.01)
喫煙 [c]		2.28	2.61		1.14 (1.11–1.17)
飲酒 [d]		2.33	2.41		1.00 (0.98–1.03)
肺がん		n=104,064	n=21,922		
職業					
ブルーカラー産業	ブルーカラー職	32.6	37.5	1.00	1.00
	サービス職	10.6	10.6	0.87 (0.83–0.93)	0.86 (0.82–0.91)
	専門職	3.1	2.7	0.75 (0.68–0.84)	0.76 (0.68–0.85)
	管理職	4.0	3.9	0.86 (0.79–0.93)	0.83 (0.76–0.90)
サービス産業	ブルーカラー職	2.8	2.9	0.89 (0.81–0.98)	0.89 (0.81–0.98)
	サービス職	10.0	9.4	0.82 (0.77–0.87)	0.83 (0.78–0.89)
	専門職	0.9	0.7	0.65 (0.54–0.77)	0.68 (0.56–0.82)
	管理職	2.0	1.9	0.80 (0.71–0.90)	0.81 (0.72–0.92)
ホワイトカラー産業	ブルーカラー職	1.7	1.5	0.76 (0.66–0.88)	0.79 (0.69–0.91)
	サービス職	6.3	5.4	0.75 (0.68–0.82)	0.77 (0.70–0.84)
	専門職	4.6	3.2	0.61 (0.55–0.66)	0.66 (0.60–0.73)
	管理職	1.4	1.0	0.61 (0.51–0.72)	0.66 (0.55–0.79)
その他		19.8	19.2	0.82 (0.79–0.86)	0.90 (0.86–0.95)
喫煙 [c]		2.33	3.04		1.36 (1.35–1.38)
飲酒 [d]		2.31	2.43		0.99 (0.98–1.00)
前立腺がん		n=136,573	n=28,392		
職業					
ブルーカラー産業	ブルーカラー職	31.5	31.8	1.00	1.00
	サービス職	11.4	12.0	1.06 (1.01–1.12)	1.06 (1.01–1.12)
	専門職	3.5	3.6	1.06 (0.99–1.15)	1.06 (0.98–1.14)

	管理職	3.9	3.9	1.02 (0.94–1.10)	1.02 (0.94–1.10)
サービス産業	ブルーカラー職	3.0	2.7	0.90 (0.82–0.99)	0.91 (0.83–0.99)
	サービス職	10.4	10.1	0.97 (0.91–1.03)	0.97 (0.91–1.03)
	専門職	1.1	1.1	0.98 (0.86–1.11)	0.98 (0.86–1.11)
	管理職	2.1	2.0	0.96 (0.86–1.06)	0.96 (0.86–1.06)
ホワイトカラー産業	ブルーカラー職	1.9	2.0	1.07 (0.96–1.20)	1.07 (0.95–1.19)
	サービス職	6.5	6.7	1.03 (0.97–1.10)	1.03 (0.97–1.10)
	専門職	4.9	5.4	1.10 (1.03–1.18)	1.10 (1.03–1.18)
	管理職	1.2	1.3	1.07 (0.94–1.22)	1.07 (0.93–1.22)
その他		18.5	17.3	0.90 (0.86–0.94)	0.90 (0.86–0.94)
喫煙 [c]		2.41	2.37		0.98 (0.97–0.99)
飲酒 [d]		2.36	2.43		1.03 (1.02–1.05)
腎がん		n=26,900	n=5,552		
職業					
ブルーカラー産業	ブルーカラー職	31.4	31.4	1.00	1.00
	サービス職	11.9	12.1	1.03 (0.93–1.14)	1.03 (0.93–1.14)
	専門職	3.8	3.8	1.04 (0.81–1.35)	1.05 (0.81–1.36)
	管理職	4.0	4.7	1.19 (1.02–1.39)	1.17 (1.00–1.37)
サービス産業	ブルーカラー職	2.9	3.1	1.07 (0.87–1.32)	1.08 (0.87–1.33)
	サービス職	11.0	10.8	0.99 (0.88–1.11)	0.99 (0.88–1.11)
	専門職	0.9	1.0	1.17 (0.81–1.67)	1.17 (0.82–1.67)
	管理職	2.0	2.3	1.15 (0.93–1.42)	1.15 (0.92–1.42)
ホワイトカラー産業	ブルーカラー職	2.1	1.7	0.84 (0.65–1.09)	0.84 (0.65–1.10)
	サービス職	7.2	7.3	1.02 (0.88–1.17)	1.03 (0.89–1.18)
	専門職	5.3	5.4	1.04 (0.88–1.22)	1.07 (0.90–1.26)
	管理職	1.4	1.4	0.97 (0.72–1.29)	0.97 (0.73–1.30)
その他		16.1	15.1	0.93 (0.82–1.04)	0.95 (0.85–1.07)
喫煙 [c]		2.35	2.58		1.08 (1.06–1.11)
飲酒 [d]		2.41	2.58		1.05 (1.03–1.08)
膀胱がん		n=64,871	n=13,590		
職業					
ブルーカラー産業	ブルーカラー職	31.3	32.8	1.00	1.00
	サービス職	10.6	11.6	1.06 (0.98–1.15)	1.05 (0.97–1.14)
	専門職	3.2	3.0	0.91 (0.80–1.03)	0.90 (0.79–1.03)
	管理職	4.3	4.6	1.05 (0.95–1.16)	1.02 (0.92–1.13)
サービス産業	ブルーカラー職	2.9	2.7	0.90 (0.79–1.03)	0.90 (0.78–1.03)
	サービス職	10.1	10.4	0.99 (0.93–1.06)	1.00 (0.93–1.07)

	専門職	0.9	1.0	1.14 (0.93–1.39)	1.14 (0.92–1.40)
	管理職	2.1	2.2	1.02 (0.88–1.18)	1.02 (0.88–1.19)
ホワイトカラー産業	ブルーカラー職	1.8	1.6	0.89 (0.76–1.03)	0.89 (0.77–1.04)
	サービス職	6.7	5.9	0.84 (0.75–0.95)	0.85 (0.76–0.95)
	専門職	4.9	4.5	0.88 (0.78–0.98)	0.92 (0.82–1.02)
	管理職	1.4	1.2	0.78 (0.62–0.98)	0.78 (0.63–0.98)
その他		19.9	18.4	0.86 (0.81–0.91)	0.89 (0.84–0.94)
喫煙 [c]		2.29	2.69		1.17 (1.15–1.18)
飲酒 [d]		2.31	2.43		1.02 (1.00–1.03)
悪性リンパ腫		n=29,528	n=6,157		
職業					
ブルーカラー産業	ブルーカラー職	31.0	33.4	1.00	1.00
	サービス職	11.7	11.5	0.92 (0.83–1.02)	0.92 (0.83–1.01)
	専門職	3.8	3.4	0.82 (0.69–0.96)	0.82 (0.70–0.97)
	管理職	3.8	3.9	0.96 (0.76–1.21)	0.95 (0.75–1.20)
サービス産業	ブルーカラー職	3.1	3.8	1.14 (0.97–1.34)	1.14 (0.97–1.33)
	サービス職	11.0	10.1	0.86 (0.77–0.96)	0.86 (0.77–0.96)
	専門職	0.9	1.0	0.94 (0.68–1.30)	0.94 (0.69–1.30)
	管理職	1.9	1.9	0.92 (0.69–1.22)	0.92 (0.69–1.21)
ホワイトカラー産業	ブルーカラー職	2.0	1.8	0.82 (0.65–1.04)	0.83 (0.65–1.04)
	サービス職	7.5	6.9	0.86 (0.75–0.98)	0.86 (0.76–0.98)
	専門職	5.5	5.1	0.85 (0.72–1.01)	0.87 (0.73–1.03)
	管理職	1.4	1.2	0.85 (0.60–1.19)	0.85 (0.61–1.20)
その他		16.4	16.2	0.90 (0.82–0.99)	0.91 (0.83–1.00)
喫煙 [c]		2.30	2.44		1.06 (1.03–1.09)
飲酒 [d]		2.39	2.40		0.99 (0.97–1.02)
全がん		n=1,026,247	n=214,123		
職業					
ブルーカラー産業	ブルーカラー職	31.8	33.6	1.00	1.00
	サービス職	11.1	11.4	0.99 (0.97–1.00)	0.98 (0.96–1.00)
	専門職	3.3	3.1	0.92 (0.88–0.96)	0.92 (0.88–0.96)
	管理職	4.2	4.3	0.98 (0.96–1.01)	0.97 (0.94–0.99)
サービス産業	ブルーカラー職	2.9	3.0	0.97 (0.94–1.00)	0.97 (0.94–1.00)
	サービス職	10.6	10.6	0.95 (0.93–0.96)	0.95 (0.94–0.97)
	専門職	0.9	0.9	0.92 (0.86–0.98)	0.93 (0.87–1.00)
	管理職	2.1	2.0	0.93 (0.89–0.97)	0.93 (0.89–0.97)
ホワイトカラー産業	ブルーカラー職	1.9	1.8	0.90 (0.86–0.94)	0.90 (0.86–0.95)

	サービス職	6.9	6.3	0.88 (0.86–0.90)	0.89 (0.86–0.91)
	専門職	5.0	4.5	0.86 (0.83–0.88)	0.89 (0.86–0.92)
	管理職	1.4	1.2	0.82 (0.78–0.86)	0.83 (0.79–0.87)
その他		17.9	17.3	0.89 (0.88–0.91)	0.92 (0.91–0.94)
喫煙 [c]		2.31	2.58		1.10 (1.10–1.11)
飲酒 [d]		2.35	2.51		1.05 (1.04–1.05)

[a] 多重補完から推定

[b] 年齢、病院、入院年をマッチさせた条件付きロジスティック回帰分析を用いた（model 1）。喫煙と飲酒を追加で調整（モデル 2）

[c] Log (1 + pack-year)

[d] Log (1 + daily gram of ethanol intake)で調整

R1_表 1　各循環器疾患の分布

部位	ICD-9	ICD-10	患者数 (%)
全体	390-459	I00-I99	126,508 (100)
心疾患	410-414	I20-25	30,657 (24.2)
冠動脈疾患	413,410	I20,21	27,232 (21.5)
狭心症	413	I20	19,604 (15.5)
急性心筋梗塞	410	I21	7,628 (6.0)
脳血管疾患	430-438	I60-69	50,700 (40.1)
脳卒中	430,431,434	I60,61,63	40,407 (31.9)
くも膜下出血	430	I60	4,634 (9.1)
脳内出血	431	I61	10,098 (19.9)
脳梗塞	434	I63	21,871 (17.3)

R1_表 2　データ欠損なし群とあり群の差

変数	N (%) or mean (SD)		P 値
	欠損あり (n=68,181)	欠損なし (n=1,060,410)	
Case	25,210 (37%)	103,405 (9.8%)	<.001
女性	4,923 (7.2%)	228,412 (22%)	<.001
年齢	45 (15)	61 (12)	<.001
入院年	1998 (9)	2001 (8)	<.001

P 値は t 検定またはカイ二乗検定。入院病院の分布も異なった(P <.001)。

R1_表 3　各職業における冠動脈疾患，脳卒中，循環器疾患全体のオッズ比

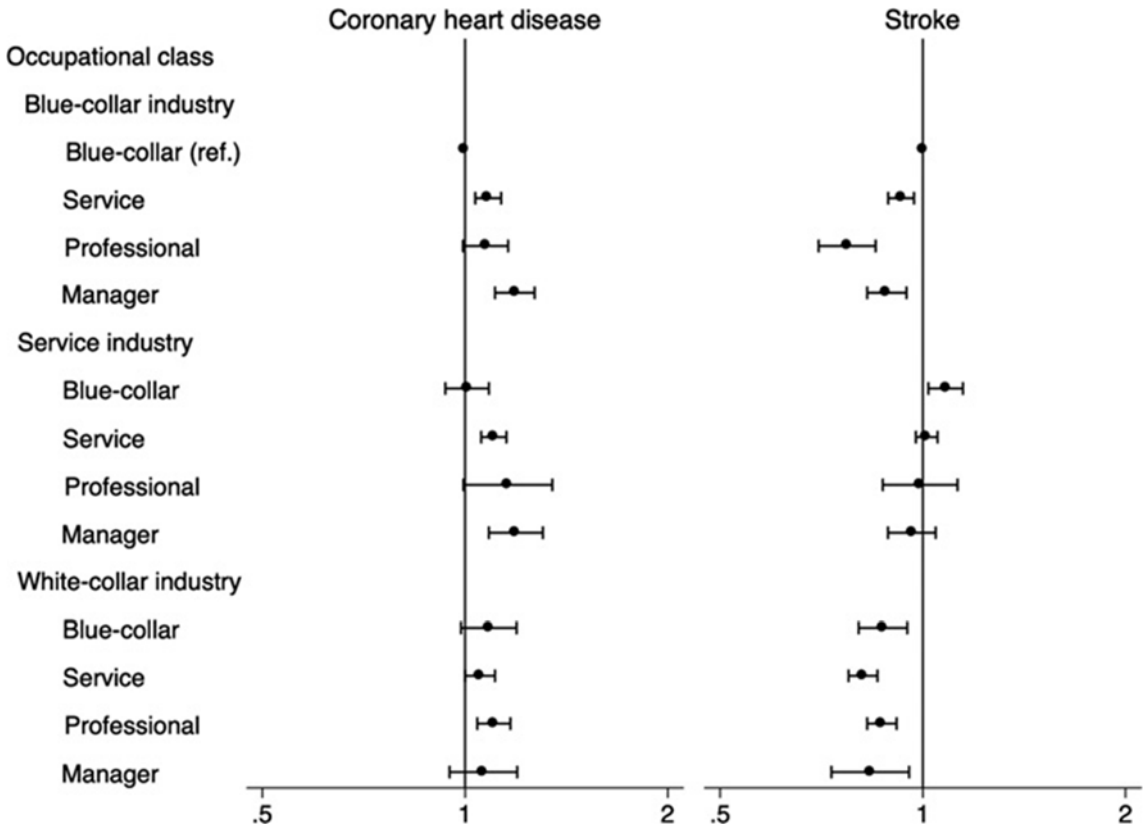
Characteristics		Control, %[a]	Case, %[a]	オッズ比（95%信頼区間）[b]	
				モデル 1	モデル 2
冠動脈疾患, n		226,378	27,452		
職業					
ブルーカラー産業	ブルーカラー職	34.6	33.6	1.00	1.00
	サービス職	13.9	13.8	1.09 (1.04–1.13)	1.08 (1.04–1.13)
	専門職	4.1	3.8	1.05 (0.97–1.13)	1.07 (0.99–1.16)
	管理職	4.5	4.9	1.19 (1.11–1.27)	1.19 (1.11–1.27)
サービス産業	ブルーカラー職	4.1	3.9	1.01 (0.94–1.09)	1.01 (0.93–1.08)
	サービス職	15.8	16.8	1.10 (1.06–1.15)	1.10 (1.06–1.15)
	専門職	0.9	0.9	1.13 (0.97–1.32)	1.16 (0.99–1.35)
	管理職	2.2	2.4	1.20 (1.09–1.31)	1.19 (1.08–1.31)
ホワイトカラー産業	ブルーカラー職	2.1	2.1	1.07 (0.98–1.18)	1.08 (0.99–1.19)
	サービス職	9.4	9.2	1.04 (0.99–1.09)	1.05 (1.00–1.11)
	専門職	7.0	7.0	1.05 (0.99–1.11)	1.10 (1.04–1.17)
	管理職	1.5	1.5	1.06 (0.94–1.19)	1.06 (0.95–1.19)
喫煙[c]		2.1	2.3		1.15 (1.14–1.16)
飲酒[c]		2.3	2.2		0.95 (0.94–0.96)
狭心症, n		163,736	19,781		
職業					
ブルーカラー産業	ブルーカラー職	34.1	32.8	1.00	1.00
	サービス職	13.9	14.1	1.12 (1.06–1.18)	1.11 (1.05–1.17)
	専門職	4.1	4.0	1.10 (1.00–1.21)	1.11 (1.02–1.22)
	管理職	4.4	4.9	1.24 (1.14–1.34)	1.23 (1.14–1.33)
サービス産業	ブルーカラー職	4.1	3.7	0.92 (0.84–1.01)	0.92 (0.84–1.01)
	サービス職	16.2	16.9	1.08 (1.03–1.14)	1.08 (1.03–1.13)
	専門職	0.9	0.9	1.13 (0.90–1.42)	1.15 (0.92–1.45)
	管理職	2.2	2.4	1.21 (1.08–1.35)	1.19 (1.07–1.34)
ホワイトカラー産業	ブルーカラー職	2.1	2.1	1.11 (0.99–1.24)	1.12 (1.00–1.25)
	サービス職	9.4	9.3	1.05 (0.99–1.11)	1.06 (1.00–1.12)
	専門職	7.1	7.4	1.08 (1.01–1.15)	1.12 (1.05–1.19)
	管理職	1.5	1.5	1.12 (0.98–1.28)	1.12 (0.98–1.28)
喫煙[c]		2.0	2.2		1.11 (1.10–1.12)
飲酒[c]		2.2	2.2		0.98 (0.97–0.99)
急性心筋梗塞		62,642	7,671		
職業					
ブルーカラー産業	ブルーカラー職	35.8	35.6	1.00	1.00
	サービス職	13.9	13.0	1.01 (0.93–1.11)	1.01 (0.92–1.10)
	専門職	4.1	3.5	0.92 (0.80–1.06)	0.97 (0.85–1.12)
	管理職	4.7	4.8	1.07 (0.95–1.21)	1.07 (0.95–1.22)
サービス産業	ブルーカラー職	3.9	4.7	1.25 (1.09–1.42)	1.25 (1.09–1.43)
	サービス職	14.6	16.3	1.16 (1.07–1.26)	1.16 (1.07–1.26)
	専門職	0.9	0.9	1.12 (0.82–1.52)	1.17 (0.86–1.59)
	管理職	2.2	2.5	1.18 (1.00–1.38)	1.18 (1.00–1.39)
ホワイトカラー産業	ブルーカラー職	2.3	2.2	0.98 (0.78–1.24)	1.00 (0.78–1.28)
	サービス職	9.4	8.9	1.01 (0.91–1.11)	1.03 (0.93–1.14)
	専門職	6.6	6.2	0.98 (0.85–1.12)	1.06 (0.92–1.23)
	管理職	1.5	1.3	0.90 (0.67–1.21)	0.92 (0.68–1.24)
喫煙[c]		2.2	2.6		1.25 (1.22–1.27)
飲酒[c]		2.4	2.1		0.88 (0.86–0.89)
脳卒中, n		*n* = 312,675	*n* = 41,038		
職業					
ブルーカラー産業	ブルーカラー職	40.1	43.0	1.00	1.00
	サービス職	12.1	11.3	0.94 (0.90–0.98)	0.93 (0.89–0.97)
	専門職	3.2	2.4	0.77 (0.70–0.85)	0.77 (0.70–0.85)

	管理職	4.0	3.6	0.91 (0.85—0.97)	0.88 (0.83—0.95)
サービス産業	ブルーカラー職	4.0	4.5	1.08 (1.02—1.15)	1.08 (1.02—1.15)
	サービス職	15.1	16.2	1.02 (0.98—1.06)	1.01 (0.98—1.05)
	専門職	0.9	0.9	0.97 (0.85—1.10)	0.99 (0.87—1.13)
	管理職	2.0	2.0	0.98 (0.90—1.06)	0.96 (0.89—1.04)
ホワイトカラー産業	ブルーカラー職	2.1	1.9	0.88 (0.81—0.95)	0.87 (0.80—0.95)
	サービス職	8.6	7.2	0.81 (0.77—0.85)	0.81 (0.78—0.86)
	専門職	6.7	6.0	0.85 (0.81—0.89)	0.87 (0.83—0.91)
	管理職	1.3	1.1	0.84 (0.74—0.96)	0.84 (0.73—0.95)
喫煙[c]		1.9	2.1		1.08 (1.07—1.09)
飲酒[c]		2.1	2.2		1.07 (1.06—1.08)
循環器疾患全体		*n* = 999,976	*n* = 128,615		
職業					
ブルーカラー産業	ブルーカラー職	35.8	37.2	1.00	1.00
	サービス職	13.0	12.4	0.99 (0.96—1.01)	0.98 (0.96—1.00)
	専門職	3.7	3.1	0.89 (0.85—0.93)	0.90 (0.86—0.93)
	管理職	4.0	3.9	1.01 (0.98—1.05)	1.00 (0.96—1.03)
サービス産業	ブルーカラー職	4.0	4.3	1.04 (1.00—1.08)	1.04 (1.00—1.08)
	サービス職	16.4	17.7	1.06 (1.03—1.08)	1.05 (1.03—1.07)
	専門職	0.9	0.9	1.01 (0.94—1.09)	1.03 (0.96—1.10)
	管理職	2.0	2.0	1.03 (0.98—1.08)	1.01 (0.96—1.06)
ホワイトカラー産業	ブルーカラー職	2.1	2.0	0.97 (0.93—1.02)	0.97 (0.93—1.02)
	サービス職	9.4	8.4	0.90 (0.88—0.92)	0.91 (0.88—0.93)
	専門職	7.4	6.9	0.91 (0.89—0.94)	0.94 (0.92—0.97)
	管理職	1.4	1.2	0.91 (0.85—0.98)	0.91 (0.85—0.98)
喫煙[c]		1.9	2.1		1.09 (1.08—1.09)
飲酒[c]		2.2	2.2		1.02 (1.02—1.03)

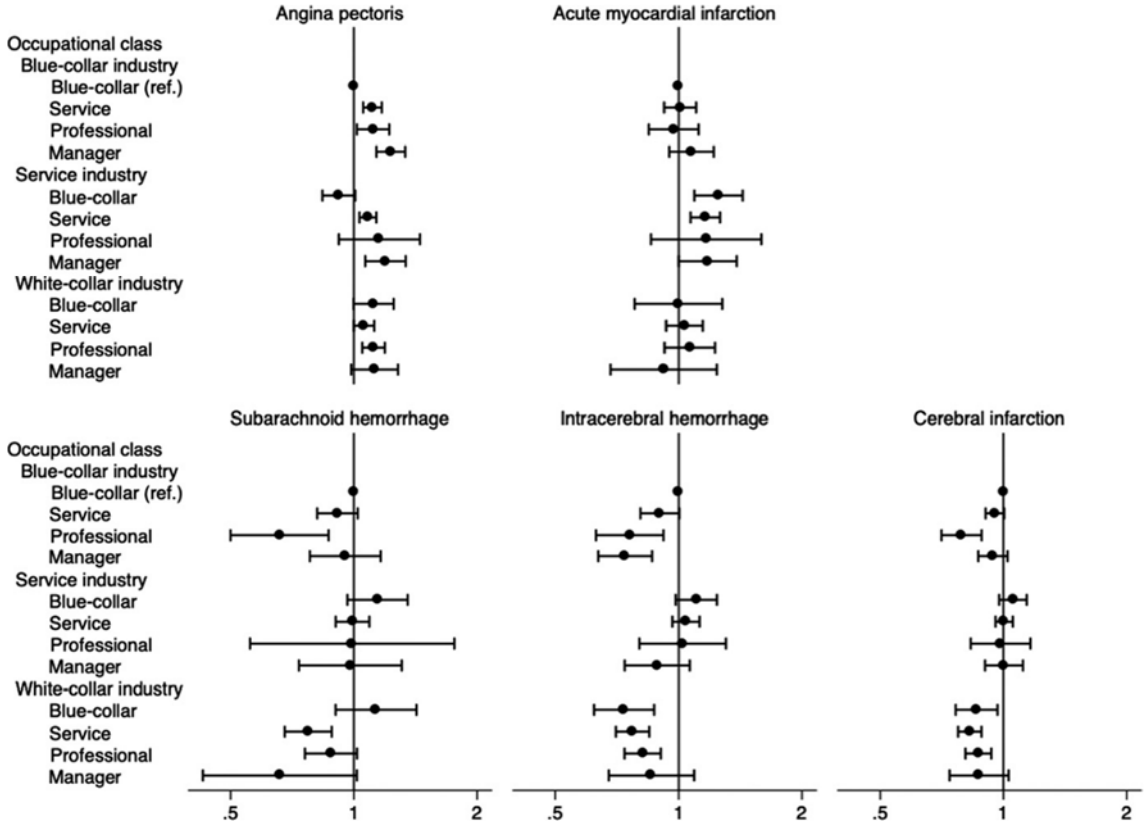
[a] 多重補完から推定

[b] 年齢，病院，入院年をマッチさせた条件付きロジスティック回帰分析を用いた（model 1）。喫煙と飲酒を追加で調整（モデル 2）

[c] Log (1 + pack-year)と Log (1 + daily gram of ethanol intake)で調整（モデル 2）



R1_図1　各職業と関連する冠動脈疾患と脳卒中のリスク。 オッズ比（点）と95%信頼区間（線）は多重補完法を用いた年齢，病院，入院施設，入院年をマッチさせた条件付きロジスティック回帰分析により，喫煙と飲酒を追加調整して求めた（*Zaitsu M, et al. Occupational Class and Risk of Cardiovascular Disease Incidence in Japan: Nationwide, Multicenter, Hospital-Based Case-Control Study. J Am Heart Assoc. 2019;8(6):e011350* より引用）。



R1_図 2　各職業と関連する狭心症，急性心筋梗塞，くも膜下出血，脳内出血，脳梗塞のリスク。オッズ比（点）と 95%信頼区間（線）は多重補完法を用いた年齢，病院，入院施設，入院年をマッチさせた条件付きロジスティック回帰分析により，喫煙と飲酒を追加調整して求めた（*Zaitsu M, et al. Occupational Class and Risk of Cardiovascular Disease Incidence in Japan: Nationwide, Multicenter, Hospital-Based Case-Control Study. J Am Heart Assoc. 2019;8(6):e011350* より引用）。

資料 1. PRTR による届出排出量・移動量の合計上位 10 物質の経年状況と都道府県別の状況

対象 10 物質の平成 13（2001）年度から平成 28（2016）年度までの全国排出量・移動量（t / 年）の推移、平成 28（2016）年度の都道府県別排出量・移動量（t / 年）を、物質ごとに示した。

1. トルエン（物質番号：300）

平成 28（2016）年度の排出量は 51,109 t / 年、移動量は 35,370 t / 年であり、排出量・移動量の合計は 86,478 t / 年であった（表 1）。「トルエン」は排出量および移動量がいずれも多い物質であった。

排出量・移動量は平成 13（2001）年度以降ほぼ一貫して減少していた。平成 28（2016）年度の排出量・移動量の合計は平成 13（2001）年度の半分程度であった（図 1）。移動量に比べ、排出量の減少が顕著であった。

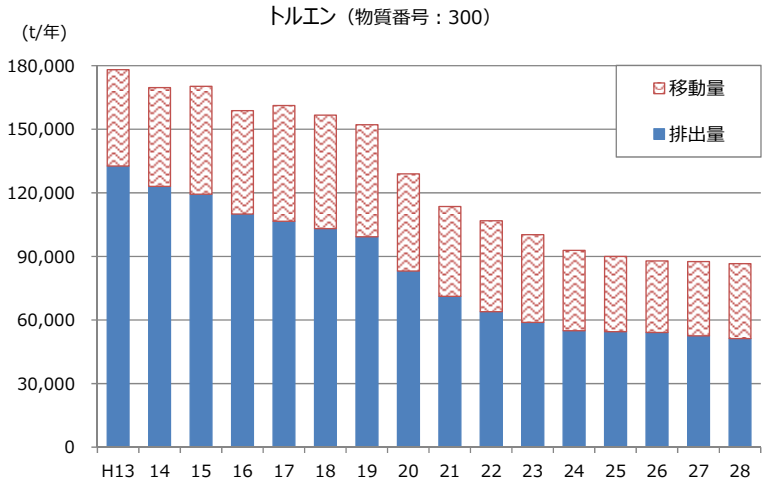


図 1. トルエンの全国排出量・移動量の推移

平成 28（2016）年度の排出量・移動量を都道府県別にみると（図 2）、排出量・移動量の合計は埼玉県、静岡県、愛知県で多く、東北地方（福島県を除く）、九州（福岡県を除く）・沖縄地方は少なかった。排出量・移動量の合計が多かった 3 県（埼玉県、静岡県、愛知県）の排出量と移動量をみると、合計が最も多かった埼玉県は移動量が多く排出量は他の 2 県（静岡県、愛知県）と同程度であった。排出量・移動量の合計が多い地域は移動量が多いという傾向は、他の都道府県でも同様にみられた。

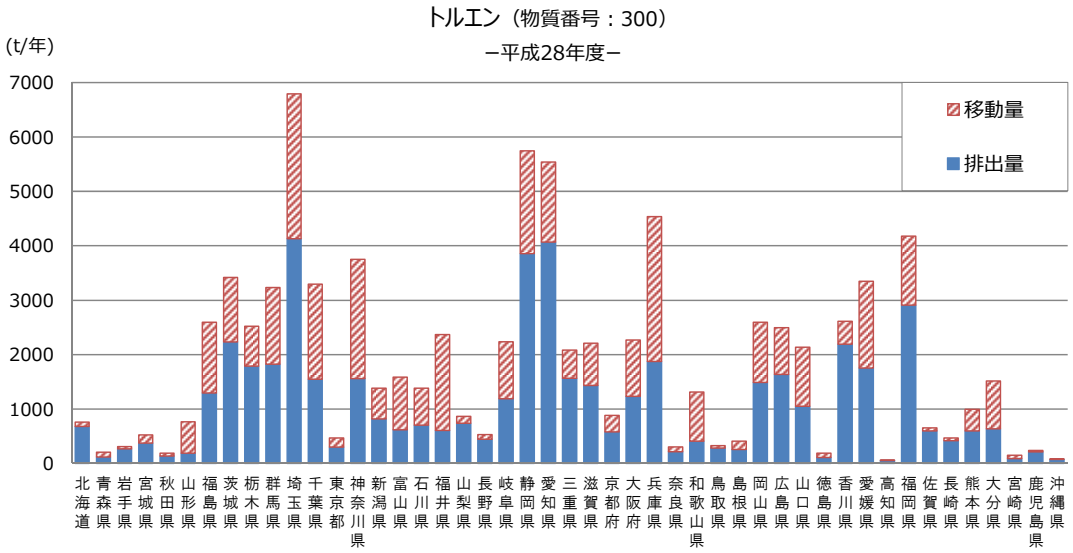


図 2. トルエンの都道府県別排出量・移動量（平成 28 年度排出分）

2. マンガン及びその化合物（物質番号：412）

平成 28（2016）年度の排出量・移動量の合計は 54,357 t / 年であった（表 1）。排出量は 2,131 t / 年であり、大部分は移動量（52,227 t / 年）であった。

排出量・移動量の推移をみると（図 3）、排出量・移動量の合計は平成 13（2001）年度から平成 15（2003）年度まで増加した後、平成 22（2010）年度まで大きな変化なく推移していた。平成 23（2011）年度に急増し、以後高止まりが続いている。平成 23（2011）年度の増加は移動量の増加によるものであり、排出量は平成 15（2003）年度以降、ほぼ毎年減少していた。

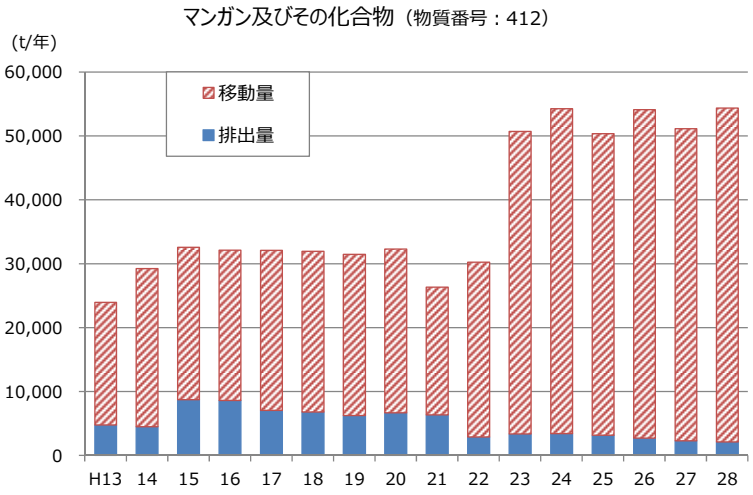


図 3. マンガン及びその化合物の全国排出量・移動量の推移

平成 28（2016）年度の排出量・移動量を都道府県別にみると（図 4）、排出量・移動量の合計は

愛知県が突出しており、続いて大阪府、岡山県、福岡県で多かった。ほとんどの都道府県で合計の大部分は移動量であった。広島県、新潟県、秋田県は、合計量は多くはないものの、他の都道府県に比べ、排出量が多かった。

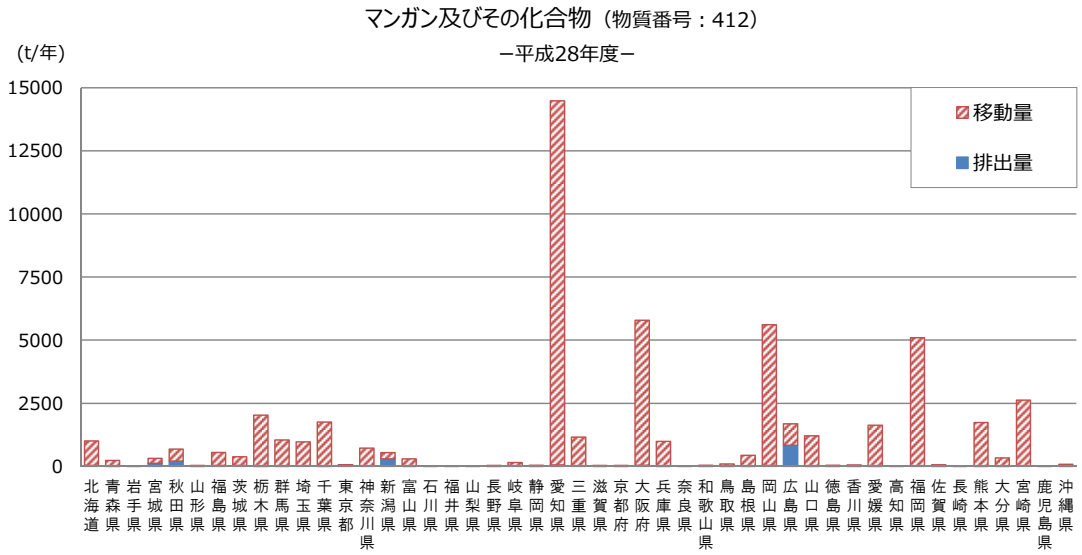


図 4. マンガン及びその化合物の都道府県別排出量・移動量（平成 28 年度排出分）

3. キシレン（物質番号：80）

平成 28（2016）年度の排出量・移動量の合計は 35,019 t / 年であり、排出量（26,939 t / 年）と移動量（8,080 t / 年）がいずれも多い物質であった（表 1）。

平成 13（2001）年度以降、排出量、移動量それぞれの減少に伴い、平成 28（2016）年度までほぼ一貫して減少していた（図 5）。

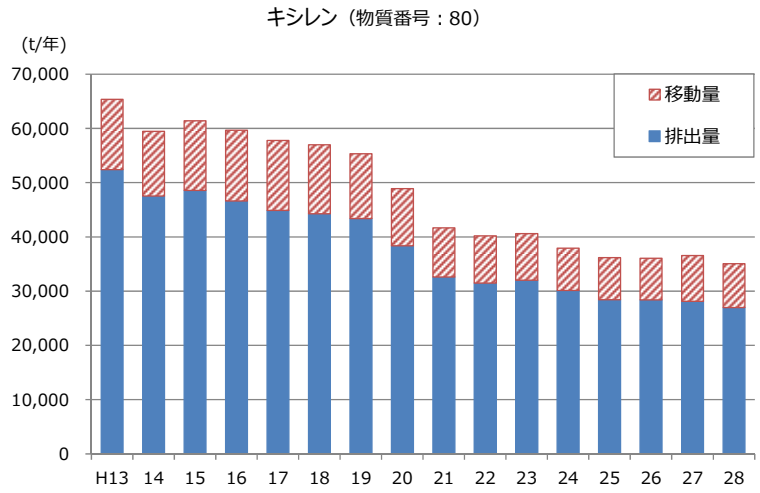


図 5. キシレンの全国排出量・移動量の推移

平成 28(2016)年度の排出量・移動量の合計は広島県、愛知県、神奈川県、愛媛県、長崎県の順に多かった(図 6)。排出量・移動量の合計が多いと移動量が多い等の一貫した関連はみられなかった。

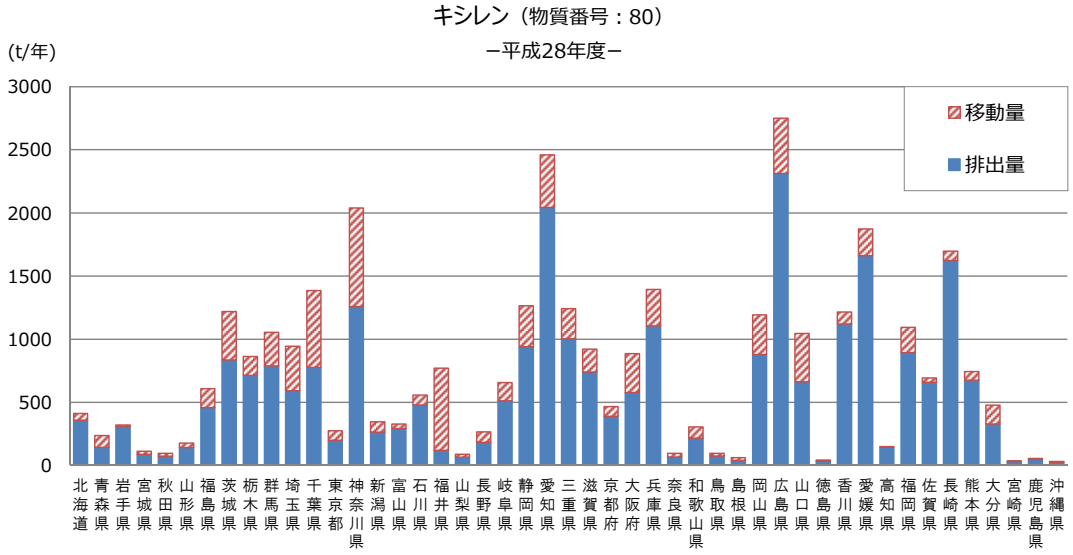


図 6. キシレンの都道府県別排出量・移動量(平成 28 年度排出分)

4. クロム及び三価クロム化合物(物質番号:87)

平成 28(2016)年度の排出量・移動量の合計は 19,154 t / 年であり、届出量のほとんどは移動量(19,024 t / 年)であった(表 1)。

排出量・移動量の合計は平成 15(2003)年度から平成 21(2009)年度まで緩やかに減少したものの、平成 22(2010)年度以降は増加していた(平成 28(2016)年度はやや減少)(図 7)。

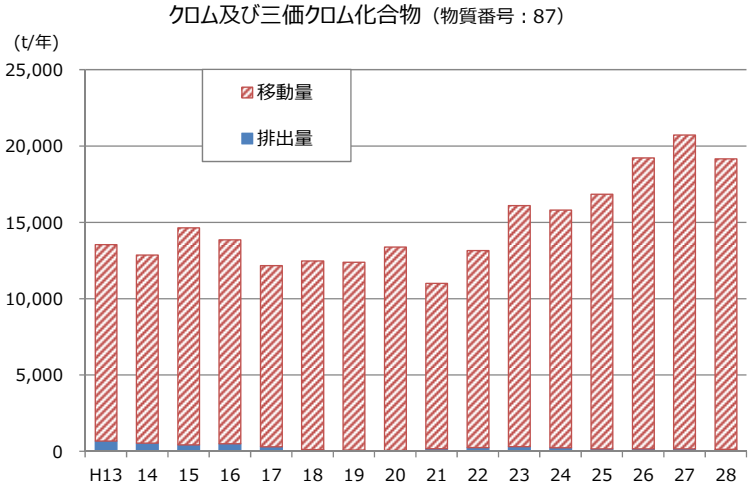


図 7. クロム及び三価クロム化合物の全国排出量･移動量の推移

都道府県別にみると（図 8）、平成 28（2016）年度の排出量･移動量の合計は愛知県、福岡県、山口県が突出して多かった。一方で、四国地方、九州（福岡県を除く）･沖縄地方の合計は非常に少なかった。秋田県は合計が少なかったものの、他の都道府県に比べ、排出量が多かった。

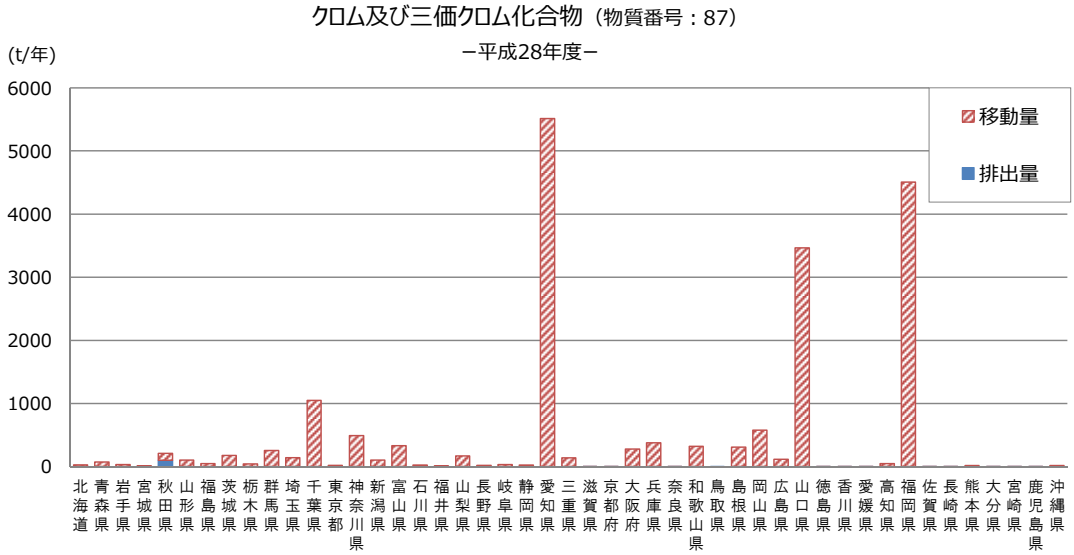


図 8. クロム及び三価クロム化合物の都道府県別排出量･移動量（平成 28 年度排出分）

5. エチルベンゼン（物質番号：53）

平成 28（2016）年度の排出量は 14,630 t / 年、移動量が 3,326 t / 年であり、排出量･移動量の合計は 17,956 t / 年であった（表 1）。

排出量･移動量の合計は平成 13（2001）年度から平成 19（2007）年度まで年々増加していた（図 10）。これをピークに平成 22（2010）年度まで減少したものの、高止まりが続いている。排出量･移動量の合計の変化は排出量の増減に依存しており、移動量はほとんど変化していなかった。

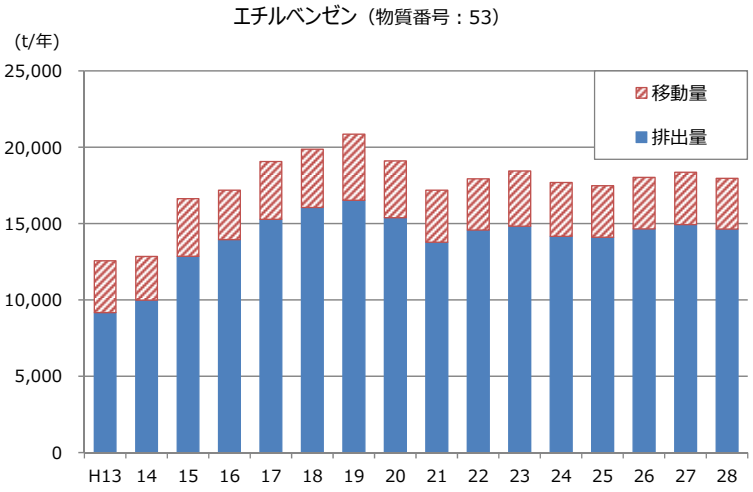


図 9. エチルベンゼンの全国排出量･移動量の推移

都道府県別にみると、排出量･移動量の合計は愛知県、広島県、長崎県、愛媛県、神奈川県で多かった（図 10）。排出量は東海･中国･四国･九州地方で多く、移動量は関東地方（栃木県、東京都を除く）で多く、排出量と移動量に一貫した関連はみられなかった。

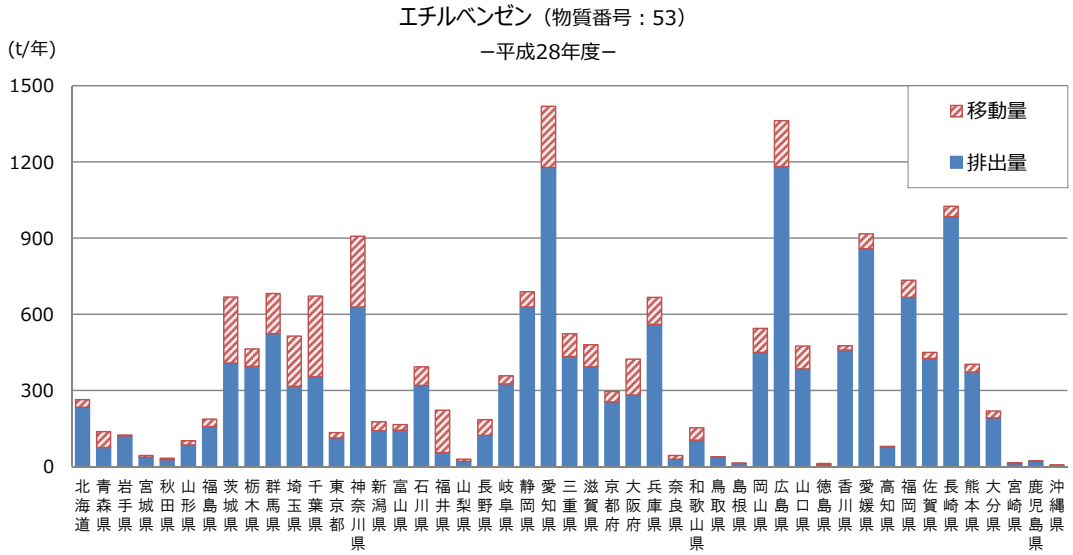


図 10. エチルベンゼンの都道府県別排出量･移動量（平成 28 年度排出分）

6. ふっ化水素及びその水溶性塩（物質番号:374）

排出量（1,977 t / 年）に比べ移動量（14,676 t / 年）が多く、平成 28 年度（2016）の排出量･移動

量の合計は 16,653 t / 年であった(表 1)。

排出量・移動量の推移をみると、(図 11)排出量・移動量の合計は平成 13(2001)年度から平成 18(2007)年度まで減少していた。その後は年々増加し、平成 26(2014)年度に急増し、以降は漸減していた。これらの変化は移動量の増減に伴うものであり、排出量は平成 13(2001)年度以降減少していた。

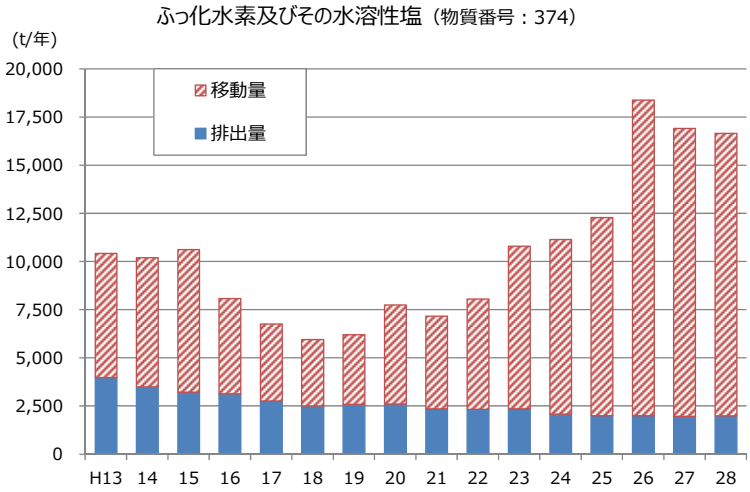


図 11. ふっ化水素及びその水溶性塩の全国排出量・移動量の推移

平成 28(2016)年度の排出量・移動量の合計を都道府県別にみると(図 12)、千葉県、大阪府、兵庫県、石川県が突出して多かった。これを除く都道府県では、排出量・移動量が少なかった。

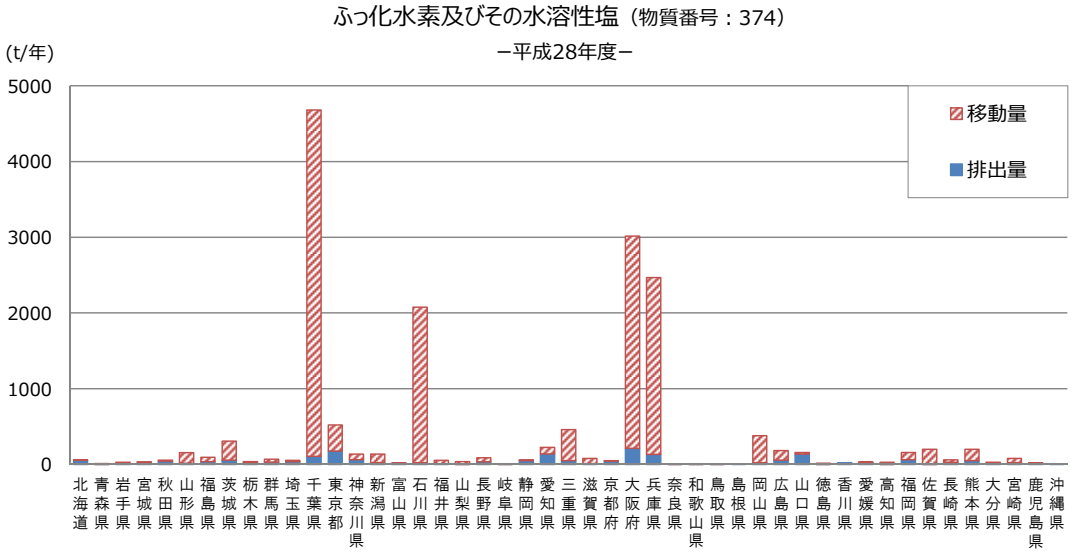


図 12. ふっ化水素及びその水溶性塩の都道府県別排出量・移動量(平成 28 年度排出分)

7. ジクロロメタン <別名：塩化メチレン>（物質番号：186）

平成 28（2016）年度の排出量は 9,896 t / 年、移動量は 6,667 t / 年であり、排出量・移動量の合計は 16,564 t / 年であった（表 1）。

平成 13（2001）年度以降、排出量・移動量の合計は年々減少しており、平成 28（2016）年度には半減していた（図 13）。排出量・移動量ともに減少しているが、移動量に比べ、排出量の減少は顕著であった。

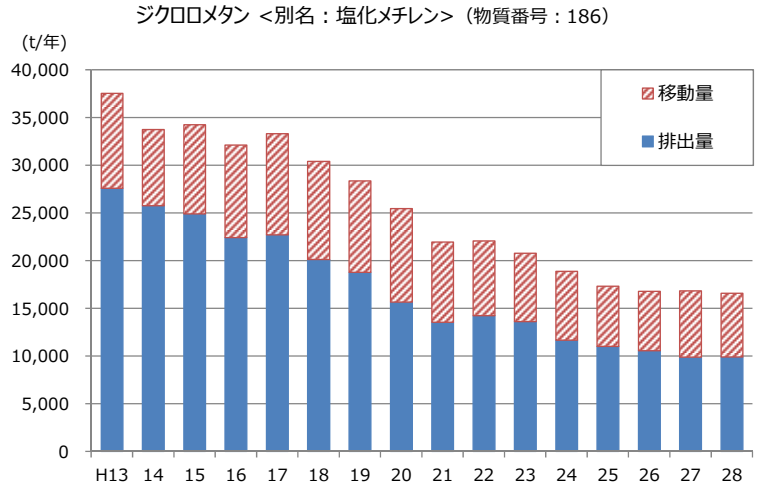


図 13. ジクロロメタン（別名：塩化メチレン）の全国排出量・移動量の推移

平成 28（2016）年度の排出量・移動量を都道府県別にみると（図 14）、排出量・移動量の合計は兵庫県、静岡県で多かった。排出量・移動量の合計が多い地域は移動量が多い傾向がみられた。

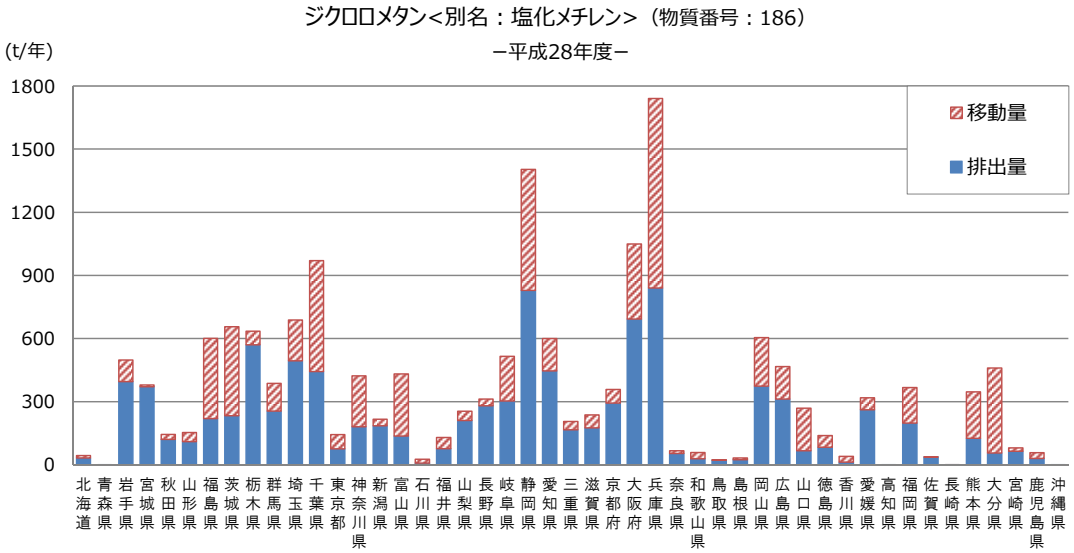


図 14. ジクロロメタン（別名：塩化メチレン）の都道府県別排出量・移動量（平成 28 年度排出分）

8. N,N-ジメチルホルムアミド（物質番号:232）

平成 28（2016）年度の排出量・移動量の合計は 9,482 t / 年であり、排出量（2,054 t / 年）に比べ移動量（7,427 t / 年）が多かった（表 1）。

平成 13（2001）年度以降、排出量・移動量の合計は緩やかに減少していた（平成 28（2016）年度はやや増加）（図 15）。平成 28（2016）年度の排出量は平成 13（2001）年度の約 1/3 であった。

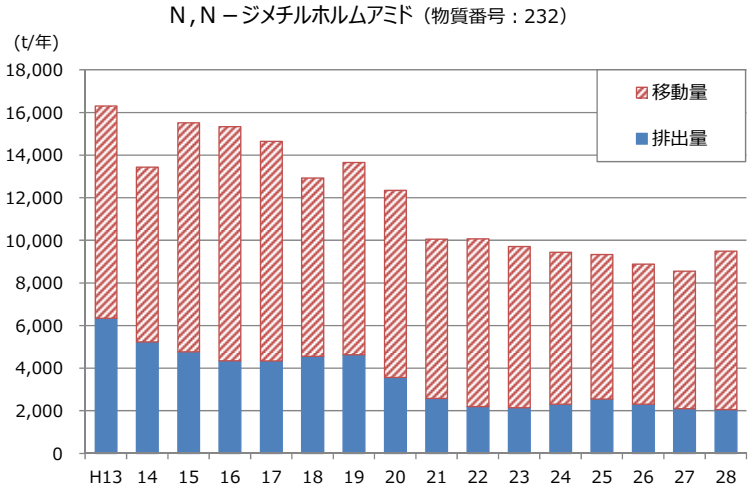


図 15. N,N-ジメチルホルムアミドの全国排出量・移動量の推移

平成 28（2016）年度の排出量・移動量を都道府県別にみると（図 16）、排出量・移動量の合計は山口県、富山県、兵庫県で多く、排出量は島根県、埼玉県で多かった。排出量・移動量が 0 または届出がなかった都道府県は、北海道、青森県、宮城県、秋田県、鳥取県、高知県、長崎県、宮崎県、沖縄県であった。

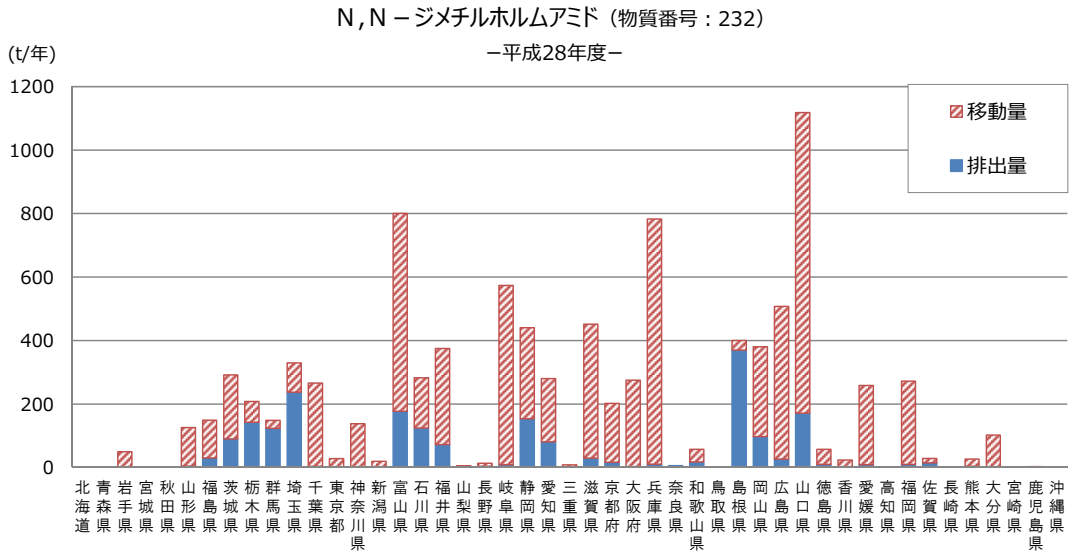


図 16. N,N-ジメチルホルムアミドの都道府県別排出量・移動量（平成 28 年度排出分）

9. 鉛及びその化合物 [鉛（物質番号：304）および 鉛化合物（物質番号：305）]

平成 28（2016）年度の排出量は 4,480 t / 年（鉛：0.8 t / 年、鉛化合物：4,479 t / 年）、移動量は 4,296 t / 年（鉛：174 t / 年、鉛化合物：4,122 t / 年）であり、排出量・移動量の合計は 8,602 t / 年（鉛：175 t / 年、鉛化合物：8,602 t / 年）であった（表 1）。

排出量・移動量の合計は平成 13（2001）年度から平成 18（2006）年度まで大きな変化はなかったが、平成 19（2007）年度および平成 20（2008）年度に急減し、その後ほぼ横ばいで推移していた（図 17）。平成 20（2008）年度以降、移動量は減少傾向であるのに対し、排出量は増加傾向がみられた。

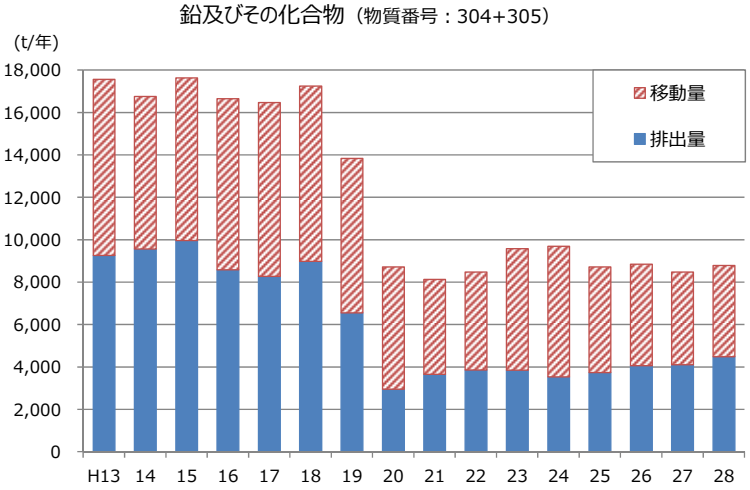


図 17. 鉛及びその化合物の全国排出量・移動量の推移

都道府県別に平成 28(2016)年度の排出量・移動量の合計をみると(図 18)、秋田県、広島県、岐阜県が突出して多かった。排出量・移動量の合計が多かった 3 県は届出量の大部分が排出量であったのに対し、合計が少ない他の都道府県はほとんどが移動量であった。

都道府県別では、排出量・移動量の合計は秋田県、広島県、岐阜県が突出して多く、その大部分は排出量であった(図 18)。排出量・移動量の合計の少ない他の都道府県は大部分が移動量であった。

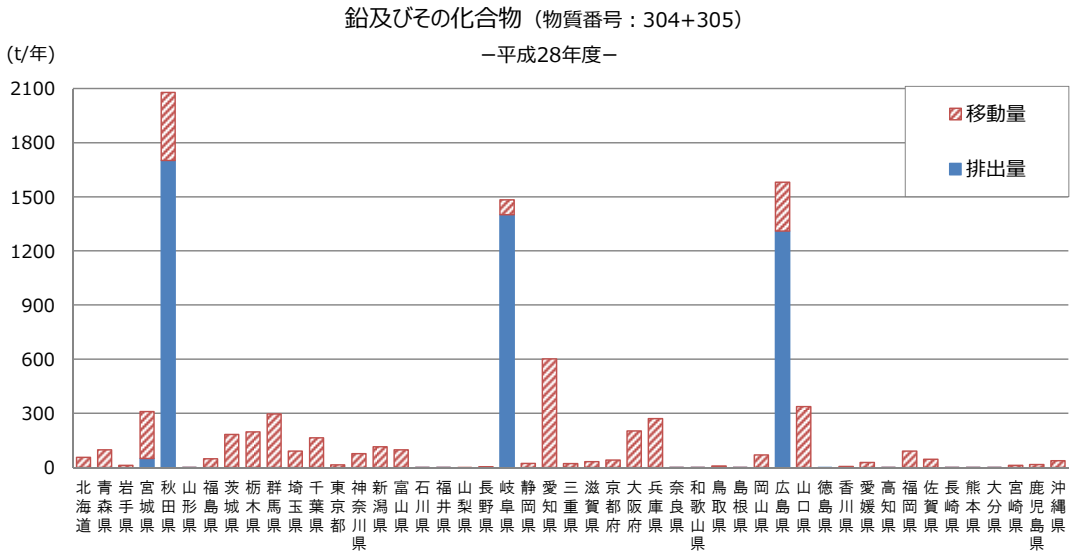


図 18. 鉛及びその化合物の都道府県別排出量・移動量(平成 28 年度排出分)

10. ほう素及びその化合物 (物質番号:405)

平成 28(2016)年度の排出量は 2,616 t / 年、移動量は 2,210 t / 年であり、排出量・移動量の合計は 4,826 t / 年であった(表 1)。

排出量・移動量の合計は平成 13(2001)年度以降年々増加し、平成 22(2010)年度をピークに減少に転じた(図 19)。排出量と移動量をそれぞれみると、排出量に大きな変化はみられないのに対し、移動量は合計量の変化に伴う増減がみられた。

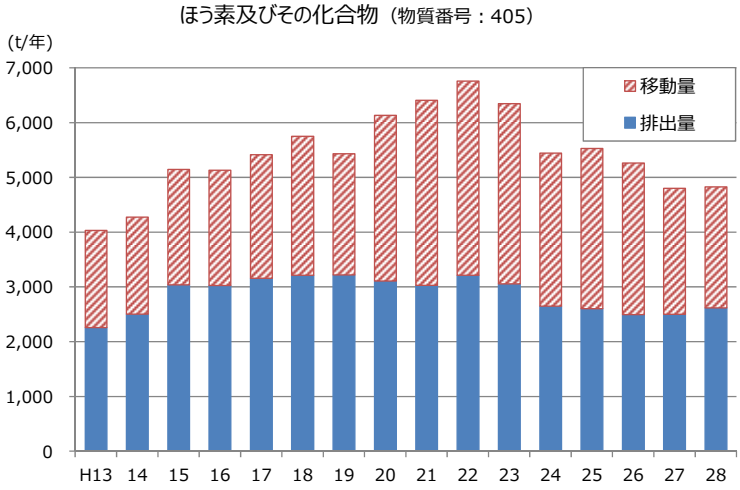


図 19. ほう素及びその化合物の全国排出量･移動量の推移

平成 28(2016)年度の排出量と移動量を都道府県別に示した(図 20)。排出量･移動量の合計は福島県、兵庫県、大阪府、千葉県、新潟県の順に多かったが、排出量は新潟県、北海道、大阪府等が多かった。

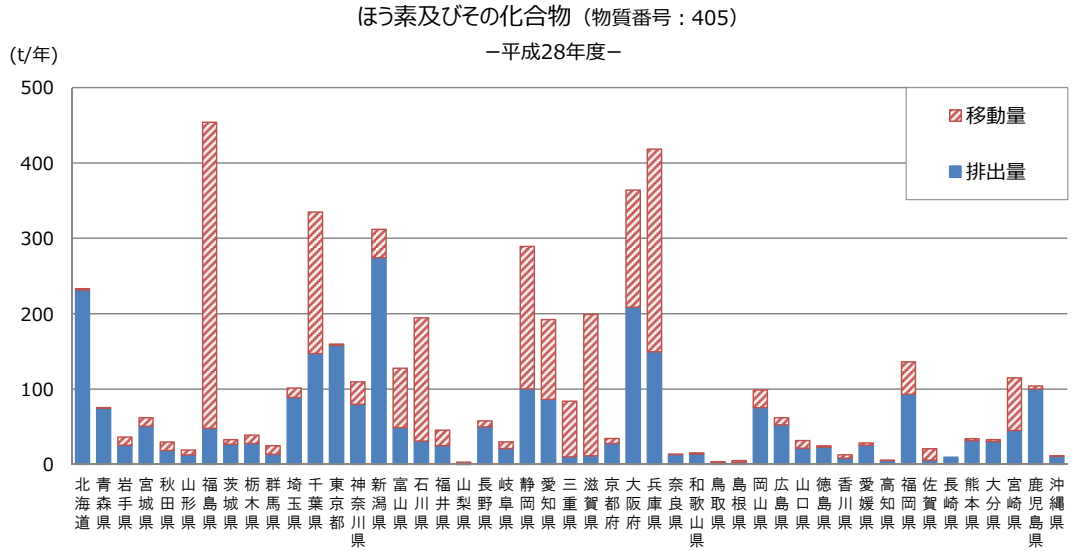


図 20. ほう素及びその化合物の都道府県別排出量･移動量(平成 28 年度排出分)

資料 2. 悪性新生物の主な部位別にみた都道府県別 SMR

悪性新生物の主な部位ごとに、平成 23(2011)年から平成 27(2015)年までの 5 年間の平均 SMR を都道府県別に示した。

1. 悪性新生物(2100)

男性の 5 年平均 SMR は北海道、青森県、秋田県で高く、長野県、沖縄県、福井県で低かった(図 21)。女性の 5 年平均 SMR は青森県、北海道、福岡県で高く、長野県、岡山県、沖縄県で低かった。

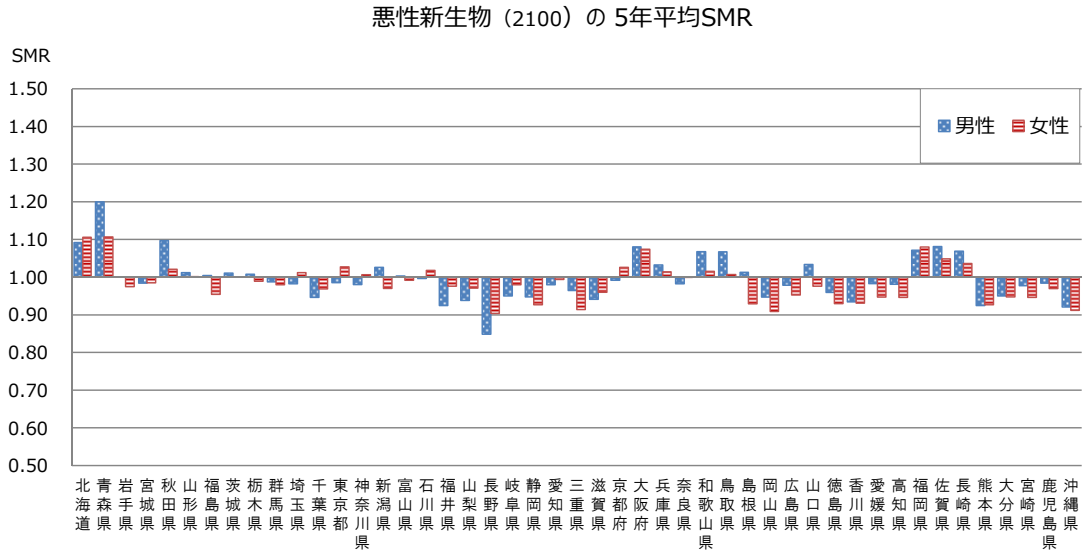


図 21. 悪性新生物による都道府県別 5 年平均 SMR(平成 23～27 年)

2. 食道の悪性新生物(2102)

食道の悪性新生物による 5 年平均 SMR は北海道・東北地方、関東地方で高く、中部地方、四国・九州・沖縄地方で低かった(図 22)。性別にみると、男性は秋田県、新潟県、東京都で高く、福井県、滋賀県、徳島県で低かった。一方、女性は東京都、神奈川県、山口県で高く、沖縄県、熊本県、大分県で低かった。

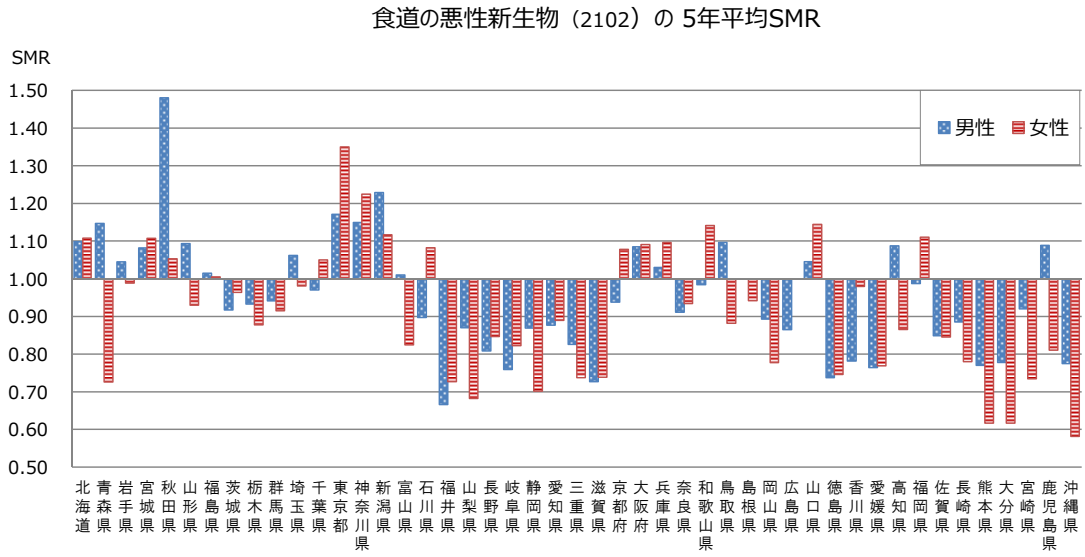


図 22. 食道の悪性新生物による都道府県別 5 年平均 SMR（平成 23～27 年）

3. 胃の悪性新生物（2103）

5 年平均 SMR は男性・女性とも東北地方（岩手県、宮城県を除く）で高く、特に秋田県、山形県、青森県（男性のみ）で高かった（図 23）。これに対し、九州・沖縄地方（佐賀県を除く）で 5 年平均 SMR は男性・女性とも低かった。

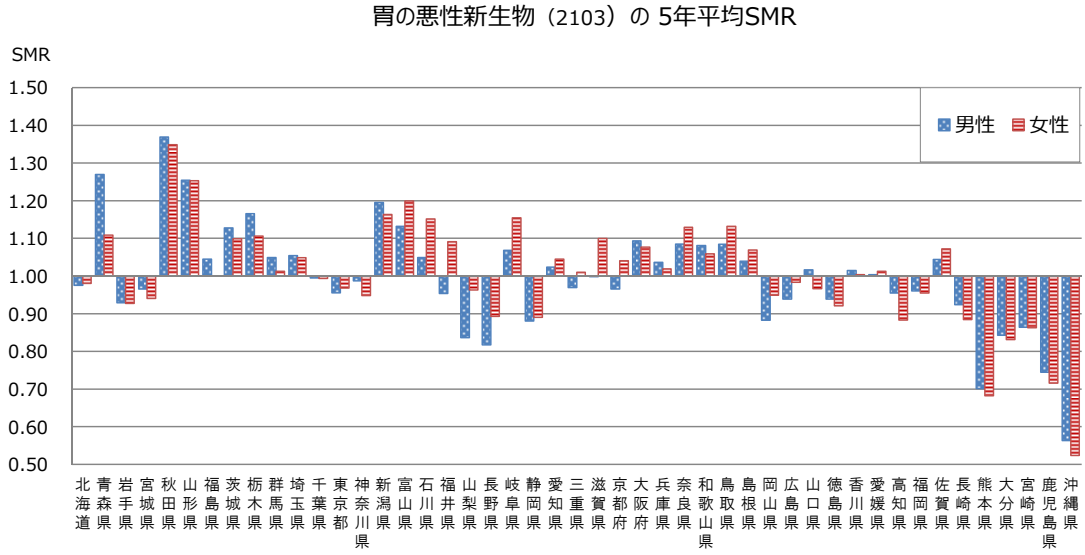


図 23. 胃の悪性新生物による都道府県別 5 年平均 SMR（平成 23～27 年）

4. 結腸の悪性新生物（2104）

5 年平均 SMR は（図 24）、男性では青森県、沖縄県で高く、岡山県、香川県で低かった。女性は青森県、秋田県で高く、大分県、愛媛県で低かった。

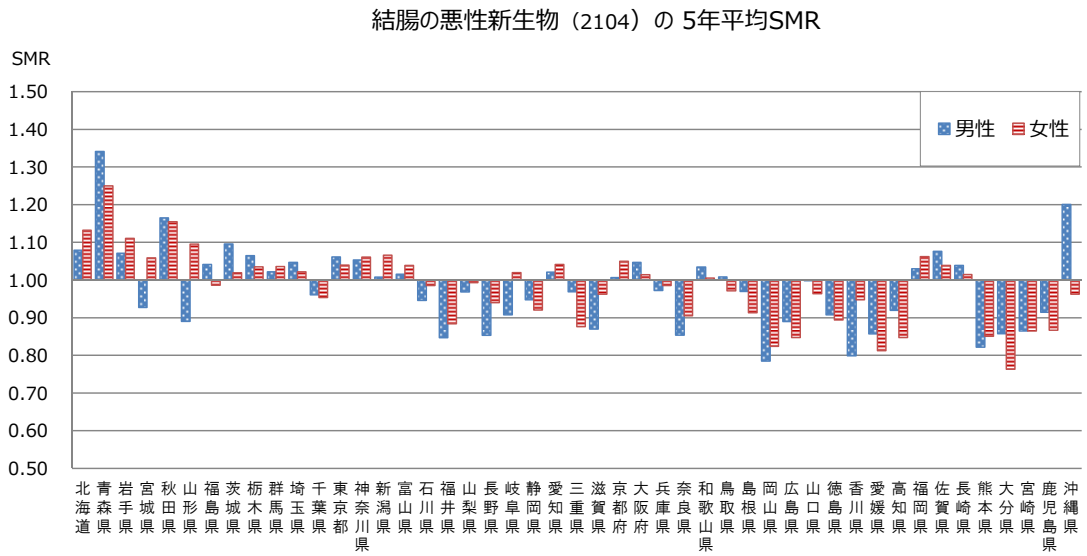


図 24. 結腸の悪性新生物による都道府県別 5 年平均 SMR（平成 23～27 年）

5. 直腸 S 状結腸移行部及び直腸の悪性新生物（2105）

青森県、岩手県は男性・女性とも 5 年平均 SMR は高かったのに対し、滋賀県、岡山県、熊本県は男性・女性とも 5 年平均 SMR が低かった（図 25）。

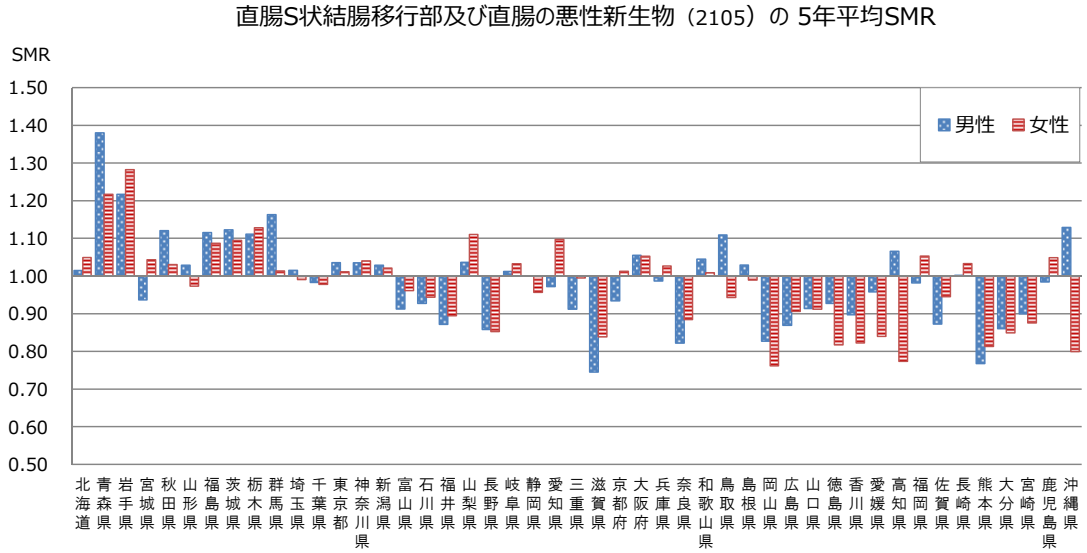


図 25. 直腸 S 状結腸移行部及び直腸の悪性新生物による都道府県別 5 年平均 SMR（平成 23～27 年）

6. 肝及び肝内胆管の悪性新生物（2106）

肝及び肝内胆管の悪性新生物は東日本で低く、西日本で高い傾向がみられた（図 26）。都道府県別の 5 年平均 SMR は男性・女性とも福岡県、佐賀県で高く、秋田県、新潟県、沖縄県で低かっ

た。

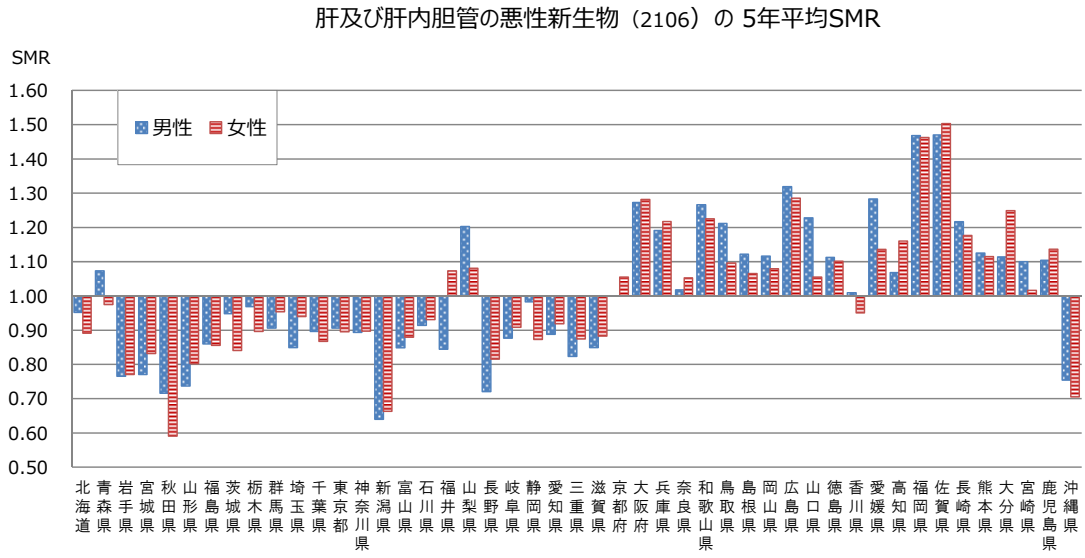


図 26. 肝及び肝内胆管の悪性新生物による都道府県別 5 年平均 SMR（平成 23～27 年）

7. 胆のう及びその他の胆道の悪性新生物（2107）

5 年平均 SMR は東北地方（宮城県を除く）で高く、特に青森県、秋田県は男性・女性とも高かった（図 27）。一方で、男性は和歌山県、奈良県で 5 年平均 SMR が低く、広島県は男性・女性とも低かった。

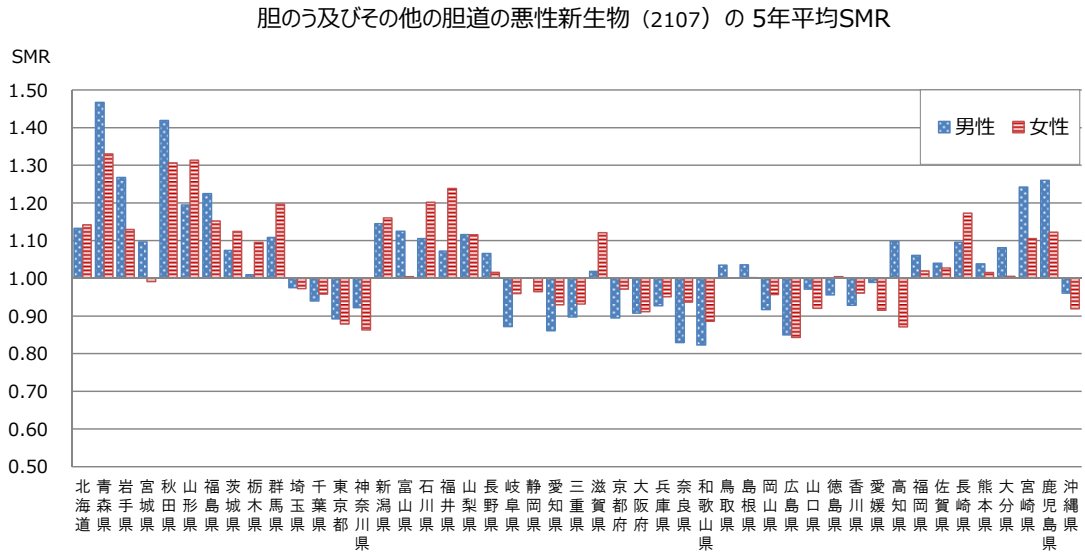


図 27. 胆のう及びその他の胆道の悪性新生物による都道府県別 5 年平均 SMR（平成 23～27 年）

8. 気管，気管支及び肺の悪性新生物（2110）

気管，気管支及び肺の悪性新生物の 5 年平均 SMR をみると（図 28）、男性は北海道、青森県で高く、長野県、山梨県で低かった。女性は北海道、大阪府で高く、長野県、島根県で低かった。北海道の 5 年平均 SMR は男性・女性とも高かったのに対し、長野県は男性・女性とも低かった。

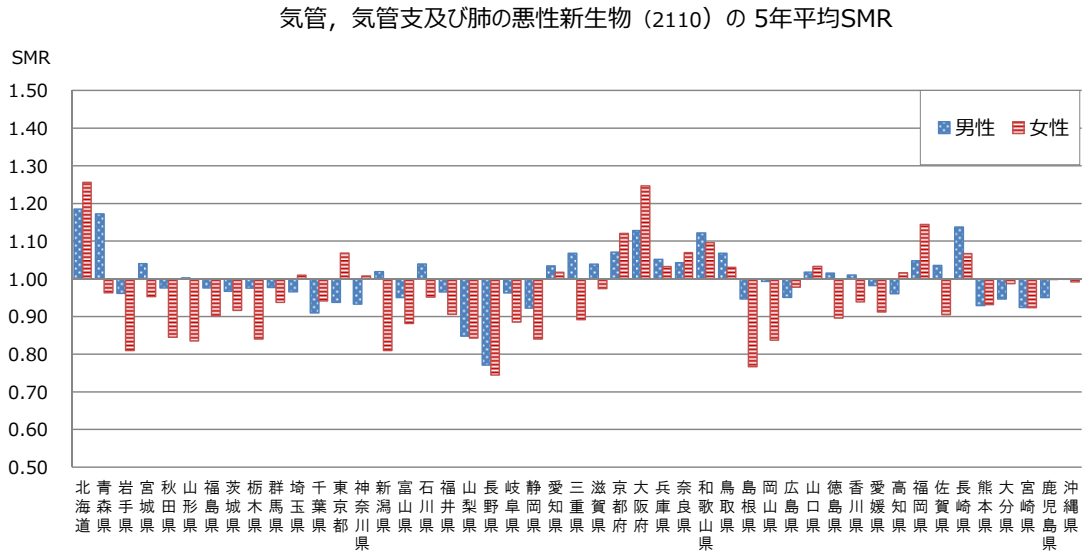


図 28. 気管，気管支及び肺の悪性新生物による都道府県別 5 年平均 SMR（平成 23～27 年）

9. 乳房の悪性新生物（2112）

女性の 5 年平均 SMR は東京都、神奈川県で高く、島根県、宮崎県で低かった（図 29）。男性は乳房の悪性新生物の罹患率が低く、5 年平均 SMR のばらつきは大きくなっていた（三重県は 0）。

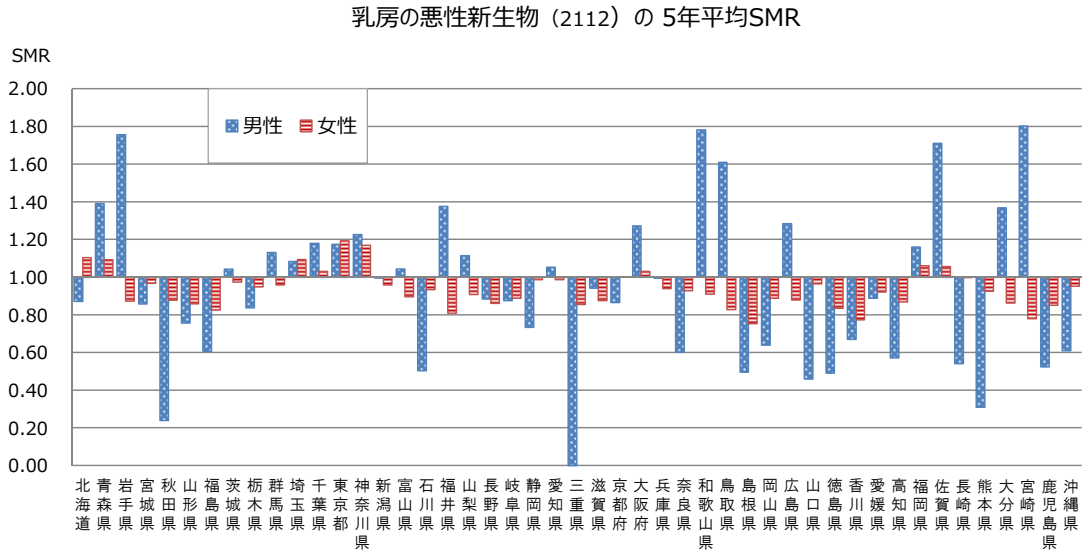


図 29. 乳房の悪性新生物による都道府県別 5 年平均 SMR（平成 23～27 年）

10. 子宮の悪性新生物(2113)

5 年平均 SMR は沖縄県が最も高く、続いて宮崎県、鳥取県の順に高かった(図 30)。これに対し、新潟県、滋賀県、島根県の順に 5 年平均 SMR は低かった。

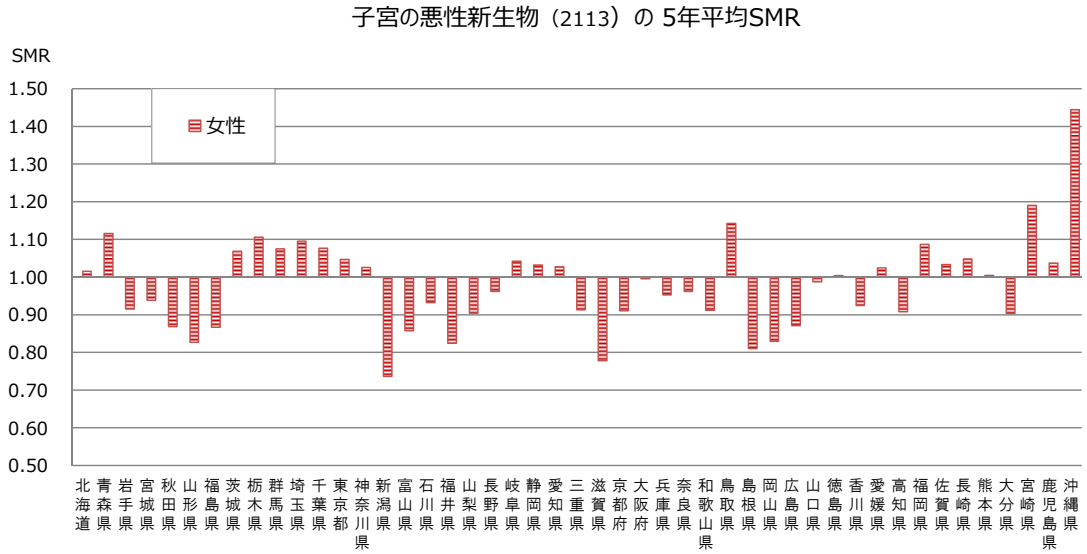


図 30. 子宮の悪性新生物による都道府県別 5 年平均 SMR(平成 23～27 年)

11. 前立腺の悪性新生物(2115)

前立腺の悪性新生物は佐賀県、青森県、福島県で 5 年平均 SMR は高かった(図 31)。一方で、香川県は 5 年平均 SMR が最も低く、次いで富山県、石川県、岡山県の順で低かった。

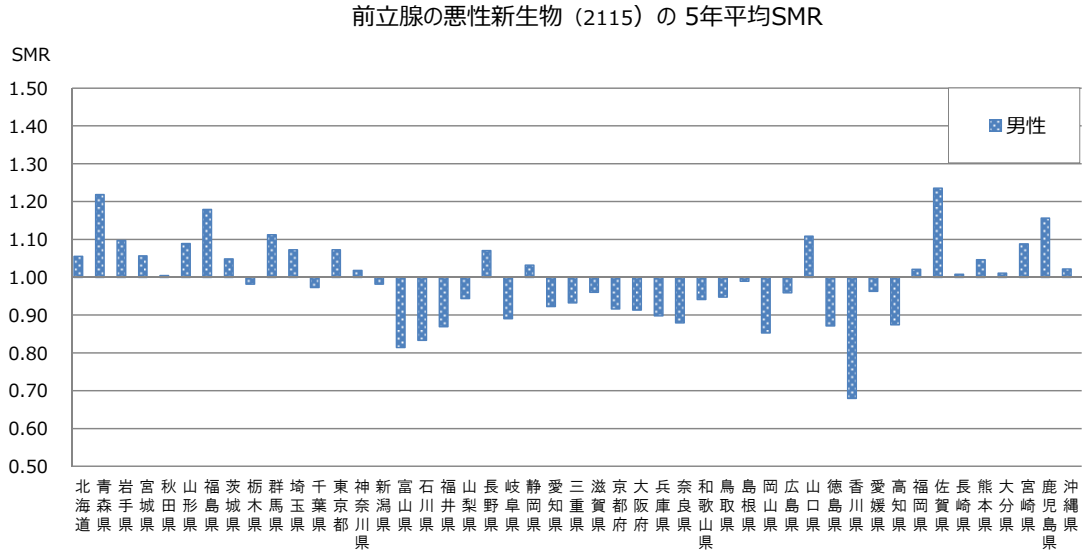


図 31. 前立腺の悪性新生物による都道府県別 5 年平均 SMR(平成 23～27 年)

12. 膀胱の悪性新生物(2116)

5 年平均 SMR は男性では島根県、青森県、山口県、女性では青森県、山形県、福岡県の順に高かった。これに対し、男性は沖縄県、香川県、愛媛県、女性は香川県、佐賀県、鳥取県で 5 年平均 SMR は低かった。青森県は男性・女性とも高く、香川県は男性・女性とも低かった。

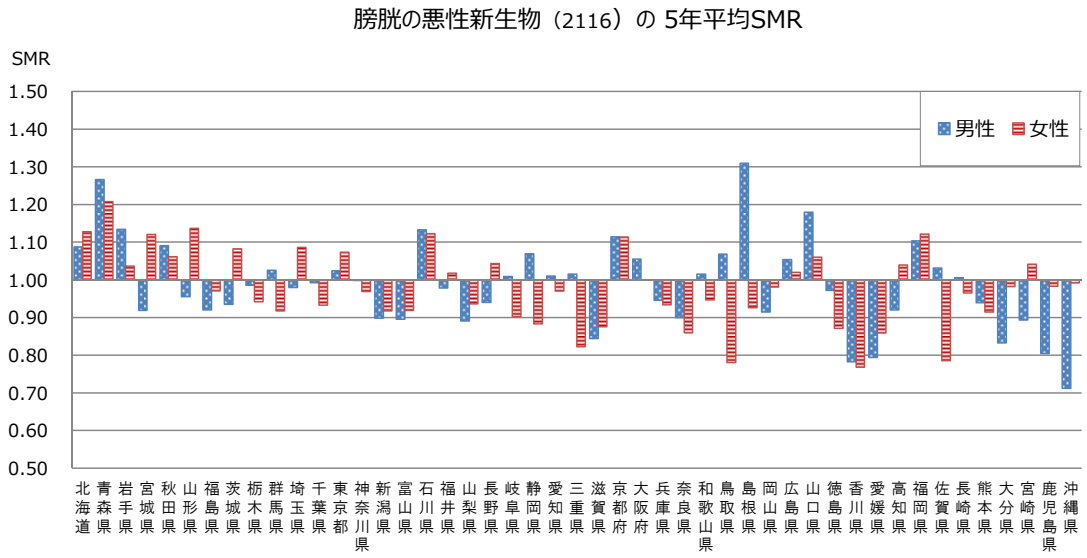


図 32. 膀胱の悪性新生物による都道府県別 5 年平均 SMR(平成 23～27 年)

13. 白血病(2116)

白血病の 5 年平均 SMR は九州・沖縄地方で高く、長崎県、宮崎県、鹿児島県、沖縄県は特に女性で高かった(図 33)。

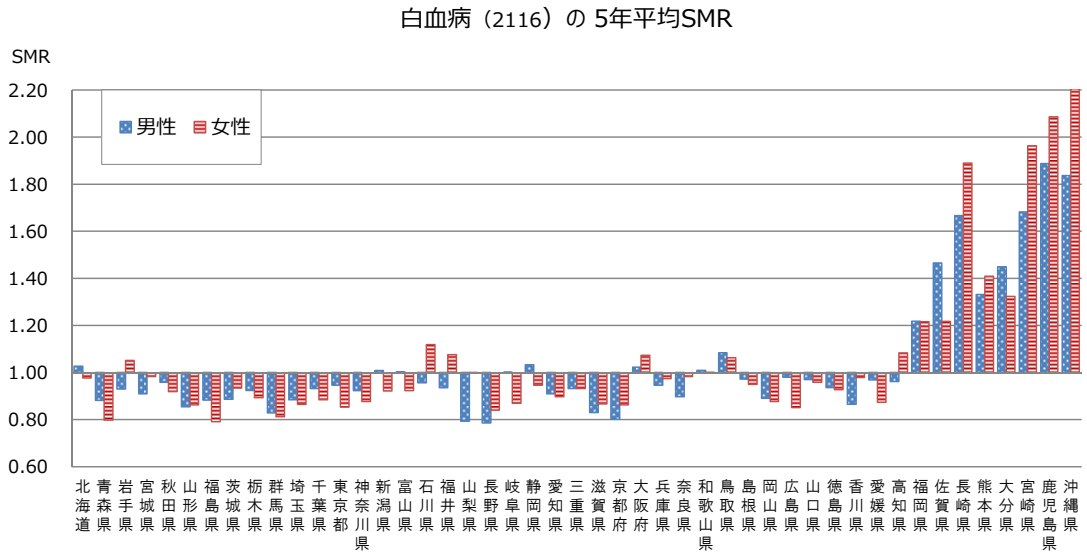


図 33. 白血病による都道府県別 5 年平均 SMR(平成 23～27 年)

資料 3　職業・産業による種々のがんの標準化罹患比（standardised incidence ratios）

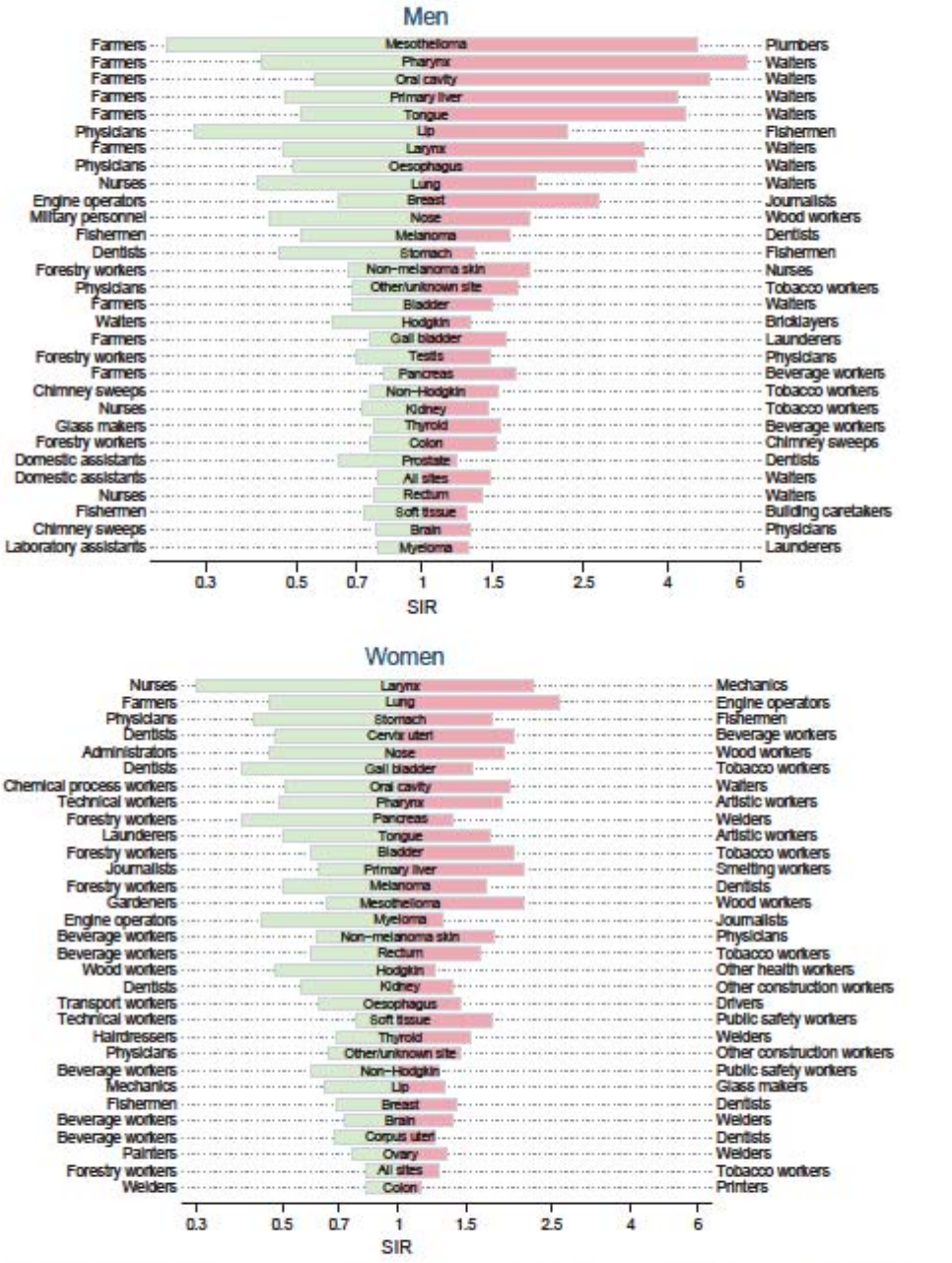


Figure 51. Risk of cancer in occupations with the highest and lowest standardised incidence ratios (SIR), by gender. Only occupations with ≥1000 workers, ≥5 observed cases and ≥5 expected cases have been included.

（出典：Pukkala E, et al. Occupation and cancer – follow-up of 15 million people in five Nordic countries. Acta Oncologica 2009; 48: p.781）

II 研究成果の刊行に関する一覧表

雑誌

発表者名	論文タイトル名	発表誌名	巻号頁	Doi	出版年
Zaitsu1 M, Cuevas AG, Trudel‐Fitzgerald C, Takeuchi T, Kobayashi Y, Kawachi I	Occupational class and risk of renal cell cancer	Health Science Reports	e49	doi: org/10. 1002/ hsr2.49	2018
Kaneko R, Sato Y, Kobayashi Y	Cholangiocarcinoma prognosis varies over time depending on tumor site and pathology	Journal of Gastrointestinal and Liver Diseases	27 (1)	59-66	2018
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金子麗奈	診断治療技術の進歩が肝臓癌の予後に与えた影響をがん登録から捉える	神奈川県のがん（神奈川県立がんセンター）		24-25	2018
Zaitsu M, Kaneko R, Takeuchi T, Sato Y, Kobayashi Y, Kawachi I	Occupational inequalities in female cancer incidence in Japan: Hospital-based matched case-control study with occupational class	SSM Population Health	5: 129-137	https://doi.org/10.1016/j.ssmph.2018.06.001	2018
Zaitsu M, Kaneko R, Takeuchi T, Sato Y, Kobayashi Y, Kawachi I	Occupational class and male cancer incidence: nationwide, multicenter, hospital-based case-control study in Japan	Cancer Medicine	8: 795-813	https://doi.org/10.1002/cam4.1945	2019

Zaitsu M, Kato S, Kim Y, Takeuchi T, Sato Y, Kobayashi Y, Kawachi I	Occupational Class and Risk of Cardiovascular Disease Incidence in Japan: Nationwide, Multicenter, Hospital-Based Case-Control Study	Journal of American Heart Association	8: e011350	DOI:10.1161/JAHA.118.011350	2019
Kaneko R, Zaitsu M, Sato Y, Kobayashi Y	Risk of cancer and longest‐held occupations in Japanese workers: a multicenter hospital‐based case‐control study	Cancer Medicine	8: 6139-6150	doi: 10.1002/cam4.2499	2019
Zaitsu M, Toyokawa S, Takeuchi T, Kobayashi Y, Kawachi I	Sex-specific analysis of renal cell carcinoma histology and survival in Japan: a population-based study 2004 to 2016	Health Science Reports	e142	doi:10.1002/hsr2.142	2019
Zaitsu M, Takeuchi T, Kobayashi Y, Kawachi I	Light to moderate amount of lifetime alcohol consumption and risk of cancer in Japan	Cancer	126(5): 1031-1040	doi:10.1002/cncr.32590	2020
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III. 研究成果の刊行物・別刷

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RESEARCH ARTICLE

WILEY Health Science Reports Open Access

Occupational class and risk of renal cell cancer

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Abstract

Objectives: We sought to examine the association between occupational class linked to job stress and the risk of renal cell cancer. To identify potential mediators, we additionally examined whether any observed associations persisted even after controlling for the contribution of stress-related factors (eg, smoking, hypertension, and obesity).

Methods: Using nationwide inpatient records (1984 to 2016) from the Rosai Hospital group in Japan, we identified 3316 cases of renal cell cancer (excluding upper tract urothelial cancer) and 168 418 controls. We classified patients' occupational class (blue-collar workers, service workers, professionals, and managers) and cross-classified it by industry type (blue-collar, service, and white-collar) based on a standardized national classification. Unconditional logistic regression with multiple imputation was used for the analyses.

Results: A significantly elevated risk of renal cell cancer was found among men in higher occupational class (eg, professionals and managers). The elevated odds in male managers across all industries persisted even after controlling for smoking and alcohol consumption, with the association being more pronounced in blue-collar industries (OR, 1.61; 95% CI, 1.34-1.93). The association appeared to be mainly mediated by hypertension.

Conclusion: Occupational class is associated with the risk of renal cell cancer in men, particularly through modifiable risk factors.

KEYWORDS

hypertension, job stress, occupational class, renal cell cancer, smoking

1 | INTRODUCTION

Renal cell cancer accounts for 2% of all malignancies in Japan, and the incidence has been increasing in recent years.[1-3] In 2013, Cancer Information Service, National Cancer Center, Japan, estimated that the total incidence of kidney cancer (including upper tract urothelial cancer) was 24 865 (16 610 male and 8 255 female).[4] Growing evidence suggests that stress-related risk factors—eg, smoking, obesity, and hypertension[5-7]—contribute to the risk of renal cell cancer.[8-14] However, very little is known of the role that stress plays in the risk of renal cell cancer, and the

Institution at which the work was performed: Harvard T.H. Chan School of Public Health, The University of Tokyo, Kanto Rosai Hospital.

association between hypertension and the risk of renal cell cancer has been previously undocumented in Japan.

Stress has long been hypothesized as a possible contributor to cancer risk via stress coping responses (ie, an increase in coping behaviors such as smoking or excess drinking), and/or direct physiological responses (eg, elevated blood pressure) that is partially mediated by activation of the sympathetic nervous system, inflammatory pathways, and the hypothalamic-pituitary-adrenal axis.[15,16] However, the empirical evidence linking various dimensions of stress to cancer incidence has remained inconsistent.[17,18] Regarding work-related stress, in the Nurses' Health Study, there was no association between multiple aspects of job stress, such as high demands and low control as well as low social support at work, and breast cancer or ovarian cancer.[19,20] Similarly, meta-analyses have not found an association between work stress and lung, colorectal, breast, or prostate cancer.[21] Yet no study to date has specifically investigated the relationship between stress because of work characteristics and renal cell cancer risk.

In Japanese society, higher occupational classes (managers and professionals) tend to report more job stress,[22,23] particularly following the collapse of the "economic bubble" in 1990. For example, Suzuki et al found that the occupational gradient in suicide in Japan reversed during the last 30 years.[22] Specifically, prior to the economic collapse of the asset bubble in 1991, suicide rates were higher among service, sales, and production workers. In the decades following the collapse, however, suicide rates have been higher among professional and managerial workers.

The distribution of job stress is markedly different in the Japanese workplace compared with the United States. For example, a recent study in Japan indicated that higher psychological distress in administrative and professional occupations is associated with increased cancer mortality at several sites.[24] Another study showed that the age-standardized suicide mortality rate increased among Japanese male administrative/managerial workers[22] between 1975 and 2005. In the same study, the lowest odds for suicide was observed among blue-collar production workers.[22] More recently, Tanaka et al[25] reported that the age-adjusted mortality rate for male managers increased across 12 types of occupation during the period of 1995 to 2010, which straddles the global economic crisis of 2008. While the magnitude of job stress across occupational classes is debated,[26,27] higher occupational class does indeed appear to be related to greater job stress in Japanese society, as indicated by the higher rates of suicide rates among managers and professionals in Japan.[22,23] Hence, in contrast to US/European studies, which typically show that job stress is higher among low-status occupations compared with high-status ones, the opposite pattern is found in Japan. Additionally, the prevalence of both hypertension and unipolar depression appeared to be higher in white-collar occupations compared with blue-collar occupations in Japan,[28,29] and hypertension appeared to be linked to job stress.[28]

In the present study, we sought to examine the association between occupational class and renal cell cancer, assuming that occupational class is a proxy for work-related stress.[30,31] In addition, we assumed that occupational class is associated with stress-related factors (smoking, hypertension, and obesity), and that these may increase the risk for renal cell cancer. Therefore, we also tested whether any observed renal cell cancer risk associated with occupational class persisted even after controlling for the potential mediation by stress-related factors.

2 | MATERIALS AND METHODS

We conducted a hospital-based case-control study using inpatient electronic medical records of the Rosai Hospital group run by the Japan Organization of Occupational Health and Safety, an

Occupational class	Japan Standard Occupational Classification	Code
Blue-collar worker	Security, agriculture, forestry, fishery, manufacturing, transport and machine operation (stationary and construction machinery operators), construction, mining, carrying, cleaning, packaging, and related workers	43–59, 64–73
Service & clercial worker	Clerical, sales, service, and transport and machine operation (railway drivers, motor vehicle drivers, ship and aircraft operators, and other transport related workers)	25–42, 60–63
Professional	Professional and engineering workers	05–24
Manager	Administrative and managerial workers	01–04
Industrial cluster	**Japan Standard Industrial Classification**	**Code**
Blue-collar industry†	Agriculture, forestry, fisheries, mining, quarrying of stone, construction, manufacturing, electricity, gas, heat supply, water, transport, and postal service	A–F, H
Service industry	Wholesale, retail trade, accommodations, eating, drinking, living-related, personal, amusement, and compound services, services not elsewhere categorized	I, M, N, Q, R
White-collar industry‡	Information, communications, finance, insurance, real estate, goods rental, leasing, education, learning support, medical, healthcare, welfare, and government except elsewhere classified	G, J, K, L, O, P, S

† Waste disposal business (Code R88) included. ‡ Political, business and cultural organizations (Code R93), railway transport (Code H42), road passenger transport (Code H43), and air transport (Code H46) included.

FIGURE 1 Occupational class cross-classified with industrial cluster

independent administrative agency. Details of the study database have been previously described.[32,33] Briefly, the Rosai Hospital group consists of 34 general hospitals in the main urban areas of Japan. Since 1984, the hospitals have recorded information on the clinical and occupational history of all inpatients. The database includes basic sociodemographic characteristics of patients, clinical diagnoses, and occupational history, as well as patients' smoking and alcohol habits, derived from questionnaires completed at the time of admission. Since 2002, pathological diagnoses have been recorded for cancer cases, while information on other risk factors (eg, hypertension, diabetes, and obesity) has been recorded since 2005. Trained registrars or nurses are responsible for registering the data. Occupational history is coded according to the standardized national classification (viz, the Japan Standard Occupational Classification and Japan Standard Industrial Classification) corresponding, respectively, to the International Standard Industrial Classification and International Standard Occupational Classification.[32,33] Written informed consent was obtained before patients completed the questionnaires.

We obtained a dataset under the research agreement between the authors and the Japan Organization of Occupational Health and Safety. The Research Ethics Committees of Graduate School of Medicine, The University of Tokyo, Tokyo (Protocol No. 3890-3) and Kanto Rosai Hospital, Kanagawa, Japan (Protocol No. 2014-38) approved the study.

2.1 | Cases and controls

The study subjects comprised 171 734 patients (3316 cases of renal cell cancer [excluding upper tract urothelial cancer] and 168 418 hospital controls) aged 20 years or older, admitted to hospitals between April 1984 and March 2016. According to available national statistics estimated with several high-quality local cancer registries in Japan, the total number of renal cell cancer cases in our data set represents 0.8% of the total incidence of kidney cancer (including upper tract urothelial cancer) in Japan for the years 1984 to 2013 (3033 of 357 993).[4]

We excluded patients with the diagnosis of upper tract urothelial cancer or patients with preexisting cancer history from the cases. Controls were patients diagnosed with musculoskeletal diseases (ICD-9, 410-739 and ICD-10, M00-M99; 89%) and skin diseases (ICD-9, 680-709 and ICD-10, L00-L99; 11%). We assumed that these diagnoses selected for the control groups were not linked to work stress.[34]

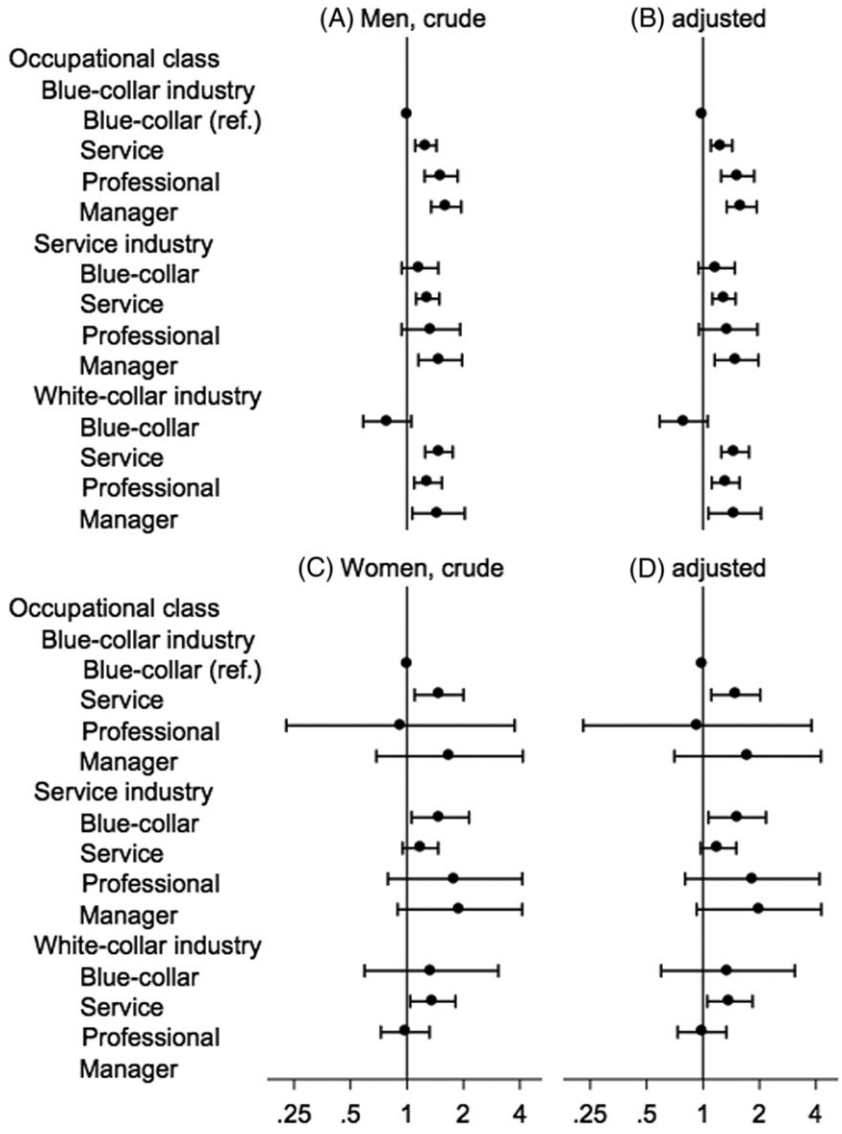

FIGURE 2 Odds ratios for renal cell cancer across different occupational classes stratified by sex. The odds ratio (dot) and 95% confidence interval (bar) were estimated by unconditional logistic regression with 5 imputed data. Male and female odds ratios were (A, C) adjusted for age and year of admission and (B, D) additionally adjusted for smoking and drinking. The numbers of cases and controls were, respectively, 2703 and 111 925 for men and 613 and 56 493 for women

TABLE 1 Odds ratios in each occupational class associated with risk for renal cell cancer

Characteristics	Control, %[a]	Case, %[a]	Odds Ratio (95% Confidence Interval)[a]		
			Model 1[b]	Model 2[c]	Model 3[c]
Men					
Total number	111 925	2703			
Occupational class					
Blue-collar industry					
Blue-collar worker	39.0	34.2	1.00	1.00	1.00
Service worker	13.5	14.2	1.26 (1.11-1.44)	1.26 (1.10-1.43)	1.26 (1.10-1.43)
Professional	4.3	5.0	1.52 (1.24-1.86)	1.53 (1.25-1.88)	1.53 (1.25-1.87)
Manager	3.2	5.8	1.62 (1.35-1.95)	1.61 (1.34-1.94)	1.61 (1.34-1.93)
Service industry					
Blue-collar worker	4.7	4.0	1.17 (0.94-1.47)	1.18 (0.94-1.47)	1.18 (0.94-1.48)
Service worker	13.4	13.2	1.29 (1.12-1.49)	1.29 (1.12-1.49)	1.29 (1.12-1.49)
Professional	1.1	1.2	1.34 (0.94-1.92)	1.36 (0.95-1.95)	1.36 (0.95-1.95)
Manager	1.6	2.7	1.50 (1.15-1.97)	1.51 (1.15-1.97)	1.51 (1.15-1.97)
White-collar industry					
Blue-collar worker	3.6	2.0	0.78 (0.58-1.05)	0.79 (0.59-1.06)	0.79 (0.59-1.06)
Service worker	8.1	9.6	1.48 (1.25-1.75)	1.48 (1.25-1.76)	1.48 (1.25-1.76)
Professional	6.5	6.5	1.29 (1.09-1.53)	1.32 (1.11-1.56)	1.32 (1.11-1.57)
Manager	1.0	1.7	1.47 (1.07-2.03)	1.48 (1.07-2.04)	1.48 (1.07-2.04)
Age, mean (SD), y	50 (17)	62 (12)	1.05 (1.04-1.05)	1.04 (1.04-1.05)	1.05 (1.04-1.05)
Year of admission, mean (SD)	2000 (8)	2003 (8)	1.02 (1.01-1.03)	1.02 (1.01-1.03)	1.02 (1.01-1.03)
Smoking					
Never	27.0	25.4		1.00	1.00
≤20 pack-year	30.3	19.9		0.93 (0.82-1.06)	0.92 (0.81-1.05)
>20-40 pack-year	25.7	29.6		1.15 (1.03-1.28)	1.13 (1.01-1.26)
>40 pack-year	16.9	25.1		1.13 (1.01-1.26)	1.10 (0.98-1.24)
Daily alcohol intakes					
Never	24.7	23.8			1.00
≤15 g	6.7	6.0			0.98 (0.79-1.20)
>15-30 g	29.3	31.7			1.07 (0.96-1.19)
>30 g	39.3	38.4			1.10 (0.96-1.25)
Women					
Total number	56 493	613			
Occupational class					
Blue-collar industry					
Blue-collar worker	28.9	28.1	1.00	1.00	1.00
Service worker	8.8	10.0	1.48 (1.10-2.00)	1.49 (1.10-2.01)	1.49 (1.11-2.02)
Professional	0.5	0.3	0.92 (0.23-3.75)	0.92 (0.23-3.76)	0.93 (0.23-3.79)
Manager	0.5	0.8	1.69 (0.69-4.15)	1.70 (0.69-4.18)	1.73 (0.70-4.25)
Service industry					
Blue-collar worker	4.5	6.4	1.50 (1.06-2.14)	1.52 (1.07-2.16)	1.52 (1.07-2.17)
Service worker	28.2	28.1	1.18 (0.95-1.47)	1.20 (0.97-1.50)	1.21 (0.97-1.50)
Professional	0.8	1.0	1.81 (0.79-4.12)	1.82 (0.80-4.14)	1.83 (0.80-4.18)
Manager	0.6	1.1	1.91 (0.89-4.11)	1.97 (0.91-4.23)	1.99 (0.92-4.27)
White-collar industry					
Blue-collar worker	0.9	1.0	1.35 (0.59-3.07)	1.35 (0.59-3.08)	1.36 (0.60-3.09)
Service worker	12.0	12.9	1.37 (1.04-1.81)	1.38 (1.05-1.82)	1.39 (1.05-1.84)
Professional	14.5	10.4	0.98 (0.73-1.32)	0.98 (0.73-1.32)	0.99 (0.73-1.33)
Manager	NA	NA	NA	NA	NA
Age, mean (SD), y	54 (17)	61 (13)	1.03 (1.02-1.03)	1.02 (1.02-1.03)	1.02 (1.02-1.03)
Year of admission, mean (SD)	2001 (9)	2003 (8)	1.04 (1.02-1.06)	1.04 (1.02-1.06)	1.04 (1.02-1.06)

(Continues)

TABLE 1 (Continued)

Characteristics	Control, %[a]	Case, %[a]	Odds Ratio (95% Confidence Interval)[a]		
			Model 1[b]	Model 2[c]	Model 3[c]
Smoking					
Never	78.6	85.0		1.00	1.00
≤20 pack-year	16.0	8.7		0.64 (0.47-0.85)	0.65 (0.48-0.88)
>20-40 pack-year	4.4	5.2		1.04 (0.72-1.49)	1.06 (0.73-1.54)
>40 pack-year	1.0	1.1		0.86 (0.41-1.83)	0.88 (0.41-1.89)
Daily alcohol intakes					
Never	68.5	74.5			1.00
≤15 g	10.2	7.2			0.81 (0.55-1.19)
>15-30 g	16.1	14.3			0.98 (0.76-1.26)
>30 g	5.2	3.9			0.89 (0.57-1.40)

Abbreviation: NA, not available.

[a]Data were estimated with 5 imputed datasets. The percentage may not total 100 because of rounding and multiple imputation. The study period from April 1984 to March 2016 was divided into 2-year financial years.

[b]Unconditional logistic regression with multiple imputation, adjusted for age and year of admission (confounders, model 1).

[c]Additional adjustment for smoking (mediators, model 2); smoking and alcohol consumption (mediators, model 3).

2.2 | Occupational class defined by occupational and industrial category

The questionnaire included questions about the patients' current job and their 3 most recent ones (including age at starting and ending). The occupations were coded with 3-digit codes in Japan Standard Occupational Classification for occupation category and 3-digit codes in Japan Standard Industrial Classification for industry category. We selected the longest held job from the history for each patient.

Owing to the enormous variety of "longest held" jobs, we aggregated the occupations into 4 occupational classes, based on previous studies[26,27,35,36]: "blue-collar workers," "service and clerical workers," "professionals," and "managers." We also categorized the longest held occupations into 3 industrial clusters based on the methodology used in a previous study[37]: "blue-collar industry," "service and sales industry," and "white-collar industry" (Figure 1). We excluded those who were not actively engaged in paid employment (eg, homemakers, students, and unemployed) in the present study. In addition, we excluded female managers in the white-collar industry because we did not observe any renal cell cancer cases in that category.

2.3 | Covariates

Age and year of hospital admission were adjusted as confounding factors. To control potential changes in diagnosis and treatments over time, we adjusted for year of hospital admission. In mediation models, we included smoking and alcohol consumption, as well as potential stress-related factors such as hypertension, obesity, and diabetes, as mediators. We assumed that occupational class is associated with stress-related risk factors (smoking, hypertension, and obesity), and that these may increase the risk for renal cell cancer.

2.4 | Statistical analysis

Among study subjects, 11% did not provide information on occupational history, smoking, and alcohol consumption and 20% did not complete all data. The background characteristics differed between those with complete and incomplete data (Table S1), and excluding incomplete data may lead to biased inference.[38,39] To deal with missing data, we performed multiple imputation for missing data among the 171 734 study subjects using all data, including occupational class, smoking, and alcohol consumption.[38-40] Five imputed datasets were generated with multiple imputation by chained equations method[39,40]; ; the following missing data were multiply imputed: occupational class (20 359, 12%), smoking (23 692, 14%), and alcohol consumption (48 608, 28%).

Using unconditional logistic regression with multiple imputation, we estimated the odds ratios (ORs) and 95% confidence intervals (CIs) for renal cell cancer in each occupational class, with blue-collar workers in the blue-collar industry as the reference group. We pooled the 5 ORs and 95% CIs obtained from each imputed dataset into one combined OR and 95% CI.[39,40] We stratified all the regression models by sex. First, we estimated the OR and 95% CI adjusted for age and year of hospital admission (model 1). Next, we adjusted for age, year of admission, and smoking (model 2). Finally, we additionally adjusted for drinking (model 3).

Owing to the data limitation that the other stress-related factors (ie, hypertension, diabetes, and obesity) were only available after 2005, we evaluated the contribution of hypertension, diabetes, and obesity among 63 704 patients admitted to hospitals after 2005 (1544 cases and 62 160 controls). The following missing data were multiply imputed: occupational class (6943, 11%), smoking (6968, 11%), alcohol consumption (19 198, 30%), hypertension (8507, 13%), diabetes (8508, 13%), and obesity (8508, 13%). In subgroup analysis, we checked for a mediation by hypertension diagnosis (model 4). Finally, in model 5, we controlled for all covariates for hypertension, diabetes, and obesity, as well as age, year of hospital admission, smoking, and drinking.

Owing to the selection of hospital controls that might introduce selection bias in either direction (ie, toward or away from the null), we performed sensitivity analysis with 2 different alternative control groups: (1) all available controls diagnosed with all

benign diseases (3316 cases and 1 298 207 controls) and (2) controls diagnosed with musculoskeletal disease (3316 cases and 150 210 controls). Additionally, we performed unconditional logistic regression among patients with complete data without performing multiple imputation (2496 cases and 116 139 controls diagnosed with musculoskeletal and skin diseases).

Alpha was set at 0.05, and all *P* values were 2-sided. Data were analyzed using STATA/MP13.1 (Stata-Corp LP, College Station, Texas).

3 | RESULTS

Among men, those in higher occupational class (professionals and managers) had a significantly increased risk of renal cell cancer compared with blue-collar workers across all industry types (Figure 2). In all 3 industries, men in the highest occupational groups, ie, managers, had significantly increased risk for renal cell cancer, with minimally adjusted OR ranging from 1.47 (for managers in the white-collar industry) to 1.62 (for managers in the blue-collar industry; Table 1). The observed increased OR for managers in all industries were not attenuated on adjustment for covariates and remained significantly associated with the risk for renal cell cancer on adjustment for covariates (adjusted OR ranged from 1.48 for managers in the white-collar industry to 1.61 for managers in the blue-collar industry, model 3; Table 1).

Among women, we observed marginal increases in the risks for managers (Figure 2). The results in the minimal-adjusted and full-adjusted models were similar (Table 1). The full-adjusted risk of managers and professionals in the service and sales industry were marginally elevated (model 3; Table 1).

In the subgroup analysis, the gradient of the ORs across occupational classes showed the same trend (Figure 3). Among men, lifestyle-related diseases (hypertension, diabetes, and obesity) were independently associated with the risk for renal cell cancer (eg, hypertension, OR 1.36; 95% CI, 1.20–1.54; model 5; Table 2); the elevated risk for higher occupational class was attenuated largely by adjustment for hypertension (model 4). After fully adjusting for all potential mediating factors, the risk for higher occupational class was not significant (except for professionals in blue-collar and white-collar industries; model 5). Among women, the fully adjusted risk among higher occupational class workers was not significantly elevated (Figure 3); however, the odds in the service and sales industries showed a trend suggesting

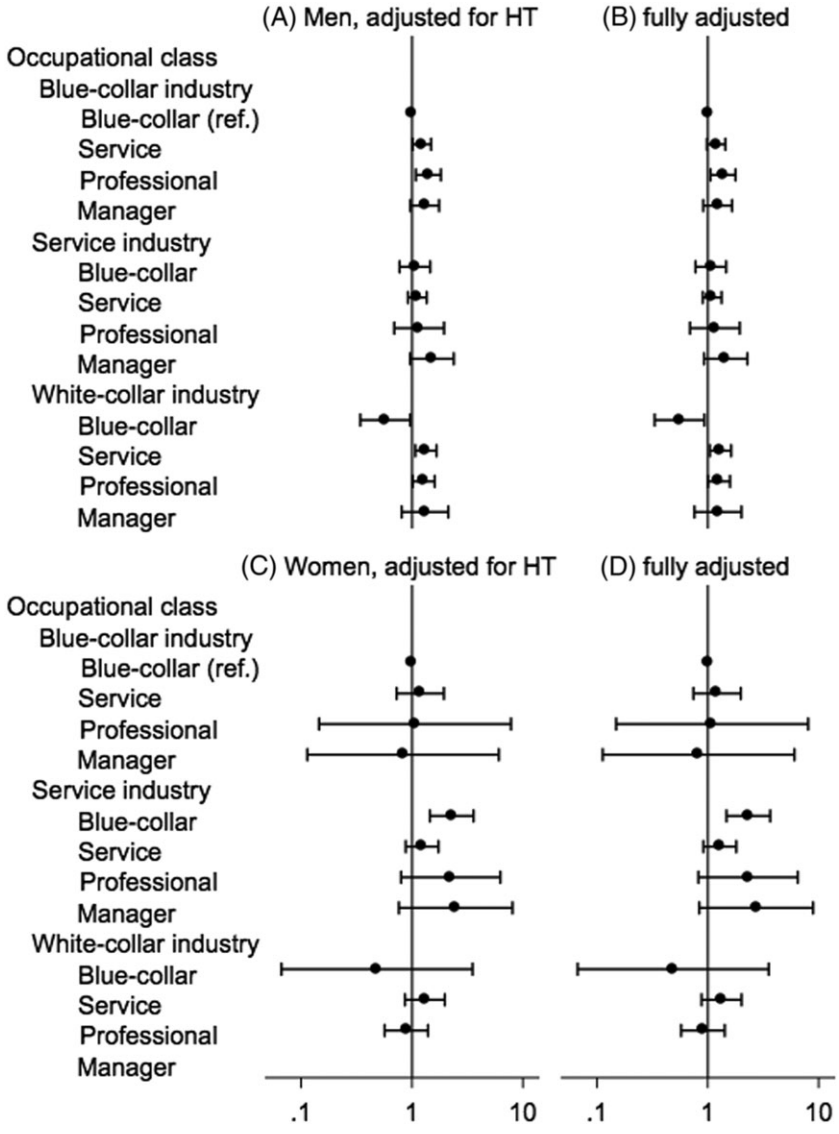

FIGURE 3 Odds ratios adjusted for hypertension and other stress-related factors in a subset data after 2005. The odds ratio (dot) and 95% confidence interval (bar) were estimated by unconditional logistic regression with 5 imputed data. Male and female odds ratios were (A, C) adjusted for age, year of admission, and hypertension and (B, D) fully adjusted for hypertension, diabetes, obesity, age, year of admission, smoking, and drinking. The numbers of cases and controls were, respectively, 1265 and 41 097 for men and 279 and 21 063 for women

TABLE 2 Subgroup analysis for mediation with hypertension and other stress-related factors after 2005

Characteristics	Control, %[a]	Case, %[a]	Odds Ratio and 95% Confidence Interval[a]	
			Model 4[b]	Model 5[c]
Men				
Total number	41 097	1265		
Occupational class				
Blue-collar industry				
Blue-collar worker	35.3	32.3	1.00	1.00
Service worker	14.1	15.7	1.22 (1.01-1.47)	1.19 (0.98-1.44)
Professional	5.0	5.9	1.39 (1.08-1.81)	1.37 (1.06-1.78)
Managers	3.0	4.4	1.28 (0.95-1.73)	1.23 (0.91-1.66)
Service industry				
Blue-collar worker	4.9	4.2	1.07 (0.78-1.47)	1.07 (0.77-1.46)
Service worker	14.0	13.0	1.11 (0.91-1.35)	1.10 (0.90-1.33)
Professional	1.2	1.3	1.17 (0.70-1.95)	1.16 (0.69-1.94)
Managers	1.5	2.6	1.49 (0.94-2.34)	1.45 (0.93-2.28)
White-collar industry				
Blue-collar worker	3.8	1.7	0.57 (0.34-0.96)	0.56 (0.33-0.93)
Service worker	8.6	9.9	1.32 (1.06-1.65)	1.30 (1.04-1.62)
Professional	7.5	7.7	1.27 (1.01-1.60)	1.26 (1.00-1.59)
Manager	1.1	1.5	1.28 (0.79-2.08)	1.24 (0.76-2.01)
Age, mean (SD), y	55 (17)	63 (12)	1.03 (1.03-1.04)	1.03 (1.03-1.04)
Year of admission, mean (SD)	2010 (3)	2010 (3)	1.05 (1.01-1.09)	1.05 (1.01-1.09)
Hypertension	27.2	42.3	1.45 (1.28-1.64)	1.36 (1.20-1.54)
Diabetes	11.3	18.2		1.27 (1.09-1.48)
Obesity	17.9	21.9		1.31 (1.12-1.52)
Smoking				
Never	21.3	19.4		1.00
≤20 pack-year	33.2	26.8		1.04 (0.87-1.24)
>20-40 pack-year	26.6	29.2		1.12 (0.95-1.33)
>40 pack-year	18.9	24.6		1.09 (0.91-1.31)
Daily alcohol intakes				
Never	18.3	17.9		1.00
≤15 g	9.1	8.5		0.98 (0.76-1.27)
>15-30 g	31.5	33.8		1.05 (0.87-1.26)
>30 g	41.1	39.8		1.03 (0.85-1.25)
Women				
Total number	21 063	279		
Occupational class				
Blue-collar industry				
Blue-collar worker	21.8	20.8	1.00	1.00
Service worker	8.4	8.2	1.20 (0.73-1.96)	1.21 (0.74-1.99)
Professional	0.5	0.4	1.06 (0.14-7.78)	1.10 (0.15-8.04)
Managers	0.4	0.4	0.83 (0.11-6.03)	0.83 (0.11-6.04)
Service industry				
Blue-collar worker	5.1	10.4	2.29 (1.45-3.60)	2.32 (1.48-3.66)
Service worker	30.3	31.2	1.24 (0.88-1.74)	1.29 (0.91-1.81)
Professional	0.8	1.4	2.25 (0.80-6.31)	2.31 (0.82-6.48)
Managers	0.4	1.1	2.51 (0.77-8.16)	2.73 (0.84-8.91)
White-collar industry				
Blue-collar worker	0.9	0.4	0.49 (0.07-3.57)	0.49 (0.07-3.55)
Service worker	14.5	14.7	1.32 (0.87-1.99)	1.33 (0.88-2.02)
Professional	16.8	11.1	0.90 (0.57-1.41)	0.90 (0.58-1.42)

(Continues)

TABLE 2 (Continued)

Characteristics	Control, %[a]	Case, %[a]	Odds Ratio and 95% Confidence Interval[a]	
			Model 4[b]	Model 5[c]
Manager			NA	NA
Age, mean (SD), y	58 (16)	62 (12)	1.02 (1.01-1.03)	1.01 (1.00-1.02)
Year of admission, mean (SD)	2010 (3)	2010 (3)	1.01 (0.94-1.09)	1.02 (0.95-1.10)
Hypertension	26.4	34.9	1.22 (0.94-1.60)	1.16 (0.89-1.52)
Diabetes	7.2	11.0		1.31 (0.88-1.95)
Obesity	16.0	19.4		1.19 (0.87-1.64)
Smoking				
Never	73.7	82.1		1.00
≤20 pack-year	19.0	9.7		0.58 (0.38-0.89)
>20-40 pack-year	6.0	7.2		1.18 (0.73-1.91)
>40 pack-year	1.4	1.1		0.69 (0.22-2.20)
Daily alcohol intakes				
Never	57.2	67.1		1.00
≤15 g	15.6	12.6		0.86 (0.56-1.34)
>15-30 g	19.9	15.1		0.81 (0.54-1.22)
>30 g	7.3	5.2		0.81 (0.44-1.47)

Abbreviation: NA, not available.

[a]Data were estimated with 5 imputed datasets with study subjects after 2005 owing to the data limitation for lifestyle-related disease (hypertension, diabetes, and obesity). The percentage may not total 100 because of rounding and multiple imputation.

[b]Unconditional logistic regression with multiple imputation, adjusted for age and year of admission (confounders) and hypertension (mediators, model 4).

[c]Additional adjustment for diabetes, obesity, smoking, and alcohol consumption (mediators, model 5).

a positive occupational gradient pattern (ie, higher risk with higher occupational class; model 5; Table 2).

In sensitivity analyses, although the precise ORs and 95% CIs differed according to the analytic model and study population, the directions of the association (ie, higher risk with higher occupational class) were identical (Figure 4 and Table S2). The result with complete data also showed the same pattern (Figure S1). The correlation between hypertension, diabetes, and obesity were all significant (pairwise correlation; all P values < .001). The profile of patients treated in Rosai hospitals appeared to be nationally representative (Table S3). The average length of longest held jobs was over 20 years (Table S4).

4 | DISCUSSION

We found an elevated risk of renal cell cancer among high status occupations (managers and professionals) in men across all industry categories, suggesting that high job stress may partially be associated with the risk of renal cell cancer. We also found, for the first time, that hypertension is a relevant independent risk factor for renal cell cancer in Japan. Furthermore, the risk for renal cell cancer associated with higher occupational class was potentially mediated through the risk for renal cell cancer associated with stress-related risk factors—viz, hypertension as well as diabetes and obesity. A similar tendency was found for women working in the service and sales industry, although the effects were marginal.

Job stress may be related to risk of renal cell cancer through both direct and indirect causal pathways. The direct pathway posits that job stress increases risk through direct biological or mechanical stimulus to cancer stem cells (eg, oxidative stress).[41,42] Although the association between occupation and renal cell cancer was substantially explained by hypertension and other potential mediators (diabetes and obesity), some significant associations in blue-collar and white-collar industries persisted among men in the present study. This residual association suggests that the direct pathway may be partially pertinent for renal cell cancer.

The indirect pathway posits that job stress may increase the risk of renal cell cancer via risk factors potentially influenced by stressful occupations, eg, cigarette smoking or the prevalence of hypertension. In fact, previous studies have suggested that psychological factors (eg, chronic or work environmental stress) can increase such lifestyle-related diseases.[43-46] In the present study, the prevalence of those who smoked more than 40 pack-years was higher in the managers than nonmanagers (25% versus 11%), and the prevalence of hypertension was greater in the managers (37% versus 27%).

In Japanese society, the concept of "hospitality" or *omotenashi* is emphasized in the service industry. Because of these expectations, those in managerial positions (or in the position of supervising other workers) may be particularly vulnerable to stress stemming from striving to meet customer expectations. In some instances, this situation has even led to death from overwork, referred to as *karoshi*. Such stress has been found to affect work-life balance among high occupational class workers.[47] By contrast, Whitehall studies showed that poorer health (eg, cardiovascular disease) is associated with low control at work,[48] which is usually the case for blue-collar workers in western contexts. Low control at work was also associated with less

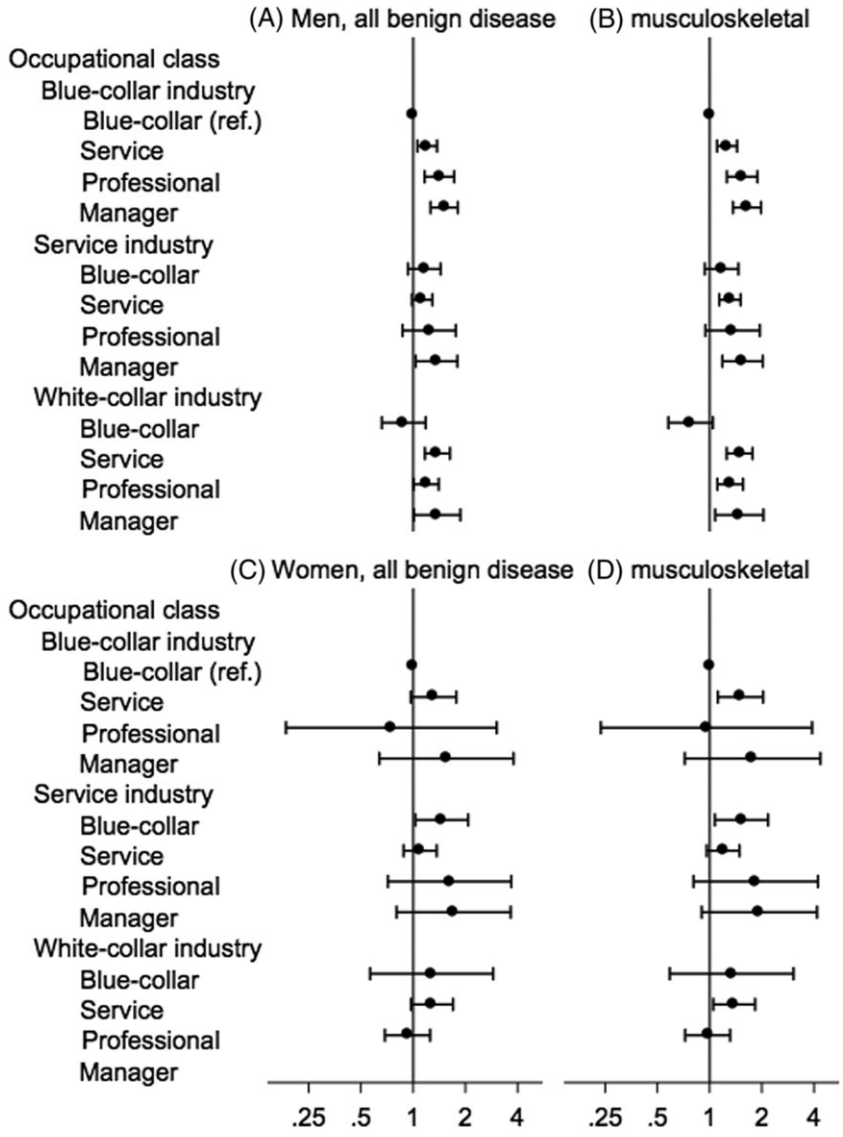

FIGURE 4 Sensitivity analysis with alternative control groups. The odds ratio (dot) and 95% confidence interval (bar) were estimated by unconditional logistic regression, adjusted for age and year of admission with 5 imputed data. Male and female control groups were, respectively, (A, C) patients diagnosed with all benign diseases and (B, D) patients diagnosed with musculoskeletal disease. The numbers of cases and controls were, respectively, as follows: (A) 2703 and 852 997 for men and (C) 613 and 445 210 for women (all benign disease controls); (B) 2703 and 99 317 for men and (D) 613 and 50 893 for women (musculoskeletal disease controls)

leisure-time physical activity.[49] Although our study is one of the largest case-control studies of renal cell cancer reported in Japan (3316 cases) and the profile of patients treated in Rosai hospitals appeared to be nationally representative[50] (Table S3), it represents less than 1% of the total incidence in the country as a whole. Hence, the generalizability of our findings to the rest of the country may be limited.

The strengths of our study include the large sample size and the detailed job information that enabled us to create occupational classes into meaningful categories by both industrial and occupational standard classifications. Another strength is the low job turn over in Japan, ie, the percentage of workers changing jobs is lower compared with other countries. In fact, prior data show that an average of 50% of men and 30% of women at their working age did not change their first job, and 20% of men and 20% of women changed only once during the age[51] from 15 to 64. Our occupational information consisted of current and up to 3 former jobs, and we chose the longest career as a proxy of job stress (the average length of longest held jobs was over 20 y; Table S4); therefore, in the sense of lifelong stress, our captured stress would be more relevant than stress measured at baseline only once in cohort studies.[21] In fact, a case-control study from Canada also found a significant association between job stress and cancer incidence at other sites.[52] Furthermore, a stressful working environment of the high occupational classes in Japan also enabled us to detect the association between higher occupational class, possibly linked to job stress, and the incidence of renal cell cancer.[22]

There are some limitations in our study. First, in any hospital-based case-control study, the selection of hospital controls may introduce selection bias in either direction (ie, toward or away from the null). However, sensitivity analysis, including controls diagnosed with all benign diseases (except malignant neoplasms) or only controls diagnosed with musculoskeletal disease, resulted in the same direction to increase the risk. Additionally, one-third of missing data may have introduced selection bias in either direction—even though the missing information were multiply imputed; however, the sensitivity analysis with complete data showed the same pattern. There might also be a potential recall bias in the self-reported information at the time of admission (eg, occupational history). However, the association of job stress and renal cell cancer was not widely known at that time. In addition, the questionnaires did not ask patients to report job stress, and the study subjects did not know the aim of our study. Therefore, the recall bias for occupational

history may not be at play between the cases and controls, and this limitation might not affect our conclusion.

Second, occupational class is not a perfect proxy for job stress, and we could not directly assess job stress because our hospital electronic medical record data did not include an assessment of stress. Higher occupational class may also reflect anxiety, depression, and other mental health conditions.[29] Kawakami et al also speculated that job commitment in these high positions might decrease the opportunities for investing in healthier behaviors such as leisure-time physical activity.[26] Physical activity has been found to be a protective factor for the risk of renal cell cancer.[53] A previous study found that the pattern of leisure-time physical activity differs in Japan compared with western contexts, viz, the highest levels of exercise were reported by clerical workers, while the lowest levels were reported among managerial workers and blue-collar workers.[54] In the same study, the highest levels of weekly physical activity, including occupational physical activity, were reported by blue-collar workers and the lowest levels among professional and managerial workers.[54] These findings suggest that higher occupational class may be associated with sedentary lifestyle behaviors, and that sedentary lifestyle may increase the risk of renal cell cancer. However, we could not assess potential mediation by physical activity/sedentary behavior because of the limitation of our dataset. Therefore, future studies should investigate the accumulation of stress on renal cell cancer, incorporating other aspects of job stress and the intervention on mental health, as well as possible residual confounding factors including physical activity, genetic, and nutrition factors, as well as dehydration.[26,54-56]

In summary, higher occupational class, which might be linked to job stress, was associated with increased odds for renal cell cancer, particularly among men, via mediation by lifestyle-related factors such as hypertension. Stress management interventions in the workplace might be a possible approach to complement existing lifestyle interventions aimed at reducing the risk of renal cell cancer.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

ETHICS APPROVAL AND INFORMED CONSENT

Written informed consent was obtained before patients completed the questionnaires. The Research Ethics Committees of Graduate School of Medicine, The University of Tokyo, Tokyo (Protocol Number 3890-3) and Kanto Rosai Hospital, Kanagawa, Japan (Protocol Number 2014-38) approved the study.

DISCLAIMER

None.

AUTHOR CONTRIBUTIONS

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SUPPORTING INFORMATION

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

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Cholangiocarcinoma Prognosis Varies over Time Depending on Tumor Site and Pathology

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ABSTRACT

Background: Cholangiocarcinoma is a relatively rare cancer that is difficult to diagnose and has a poor prognosis. Currently, knowledge concerning its etiology, tumor localization, and pathological features remains limited. The present study aimed to clarify the clinico-epidemiologic nature of cholangiocarcinoma with its clinical subtypes using the largest regional cancer registry in Japan.

Methods: Using a regional cancer registry in Kanagawa prefecture, Japan, we estimated three-year and five-year survival rates of cholangiocarcinoma patients, who were classified into two groups: intrahepatic (i-CCA) and extrahepatic cholangiocarcinoma (e-CCA) cases. The hazard ratio for each subtype, including pathological tissue type and tumor site, was calculated.

Results: During the period from 1976 to 2013, 14,287 cases of cholangiocarcinoma were identified. The prognosis markedly improved after 2006, when a new type of chemotherapy for cholangiocarcinoma was introduced in Japan. Patients with i-CCA were more likely to be younger, and less likely to undergo surgery than those with e-CCA. The prognosis of cases with i-CCA was poor compared to that of patients with e-CCA.

Conclusion: In Japan, i-CCA was more likely to develop in younger people and to have a poor prognosis. The prognosis of both i-CCA and e-CCA cases markedly improved after 2006. The present study describes clinico-epidemiological features of cholangiocarcinoma that may be useful for determining therapeutic strategies for this disease.

Key words: cholangiocarcinoma — bile duct cancer — epidemiology — survival — adenocarcinoma.

Abbreviations: CI : confidence interval; DCO: death-certificate-only; e-CCA: extrahepatic cholangiocarcinoma; i-CCA: intrahepatic cholangiocarcinoma; HR: hazard ratios.

INTRODUCTION

Cholangiocarcinoma is a cancer with a poor prognosis that arises from the cholangiocytes lining the biliary tree. Diagnosing cholangiocarcinoma is difficult and this cancer is very often fatal at the time of diagnosis due to its late clinical presentation and the absence of an effective therapeutic strategy, except for complete surgery [1]. According to the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10), cholangiocarcinoma includes intrahepatic bile duct cancer (C221), extrahepatic bile duct cancer (C240), and papillary cancer (C241). These three cancer types show different sensitivities to treatment and therefore require different therapeutic procedures.

Globally, it is well known that morbidity and mortality rates for cholangiocarcinoma are increasing [2, 3]; regional differences that originate from rural risk factors are present [4-7]. The understanding of the cell of origin, well-established risk factors, molecular pathways and interactions has increased, and advances in surgical and nonsurgical treatments for cholangiocarcinoma have resulted in improved outcomes [8-12].

Even though such progress has been reported, most clinical trials have been performed without accurate analyses of subtype profiles, such as analyzing tumor site or its pathogenesis and, therefore, the evaluation of outcomes for specific subgroups of patients with cholangiocarcinoma is totally inadequate. In particular, studies focusing on the survival rates of various tumor sites or different pathological tissue types over time are lacking.

We therefore examined the clinical and epidemiological characteristics of cholangiocarcinoma as well as the prognosis of patient subtypes according to the tumor site and pathology over time, using a large-scale cancer registry in Japan.

METHODS

Kanagawa Regional Cancer Registry

Kanagawa Prefecture is a neighbouring prefecture of Tokyo, and is the second largest in Japan, with a population of about nine million. The Prefecture started its own Regional Cancer Registry in 1970, with the accumulated number of cases being approximately 990,000 by December 31, 2013. Because the Tokyo Prefecture has only had a registry of cancer cases since 2012 and has therefore not yet accumulated substantial data, the Kanagawa Regional Cancer Registry is presently the largest regional cancer registry in Japan. Details on the cancer registry system in Japan have been reported elsewhere [13]. Data was collected from neoplasm registration sheets reported by each diagnosing hospital or from clinics and death certificates of residents in Kanagawa Prefecture. The Kanagawa Prefectural Cancer Center collected and consolidated the data into anonymous formats and made these available for academic and administrative purposes.

Accumulated data include the following items: 1) personal identification code, 2) method of registry entry, 3) diagnosing institution, 4) sex, 5) date of birth, 6) date of diagnosis, 7) local government code for the patient's home address, 8) ICD-10 code for disease name, 9) ICD-O-3 code for pathology, 10) initial or recurrent tumour, 11) therapeutic strategy (very brief), 12) operative procedure (if any), 13) date of death, 14) cause of death, 15) date of last follow-up, and 16) TNM classification and pathological grade according to ICD-O-3 in diagnosed patients. The reporting of TNM classifications became mandatory in 2005.

All information was collected by persons trained in Japan by the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute in the US. Information was updated every year from vital statistics and death certificates. Previous versions of pathological codes were transformed to the latest versions through standardized regulations consistent with changes in coding practices for cholangiocarcinoma. The proportion of death-certificate-only (DCO) cases in the whole database was 18.2% by the end of 2013 [14].

Subject and classification method

We obtained clinical data relating to gastrointestinal cancers between June 15, 1954 and December 30, 2013 in an anonymous format under a research agreement with the Kanagawa Prefectural Cancer Center. From such data, intrahepatic bile duct (C221), extrahepatic bile duct (C240), and papillary cancers (C241), according to ICD-10, were extracted and included in this study. Gall bladder cancer (C230) was excluded from the analysis, based on current guidelines for the diagnosis and treatment of cholangiocarcinoma [15].

In order to determine the trend in patient survival rates throughout the entire analysis period, the three-year survival rate of patients was calculated every two years. Because the number of registrations for cholangiocarcinoma before 1975 was small, we excluded these data.

With regard to the five-year survival rate, we divided the whole study period into Period 1 (from 1976 until 2006), before the introduction of new regimens of chemotherapy (such as gemcitabine, tegafur/gimeracil/oteracil or cisplatin) for the treatment of cholangiocarcinoma in Japan, and Period 2 (from 2006 to 2013), after the approval of new regimens.

Regarding the location of tumors, C221 was defined as an intrahepatic cholangiocarcinoma (i-CCA), and C240 and C241 were defined as extrahepatic cholangiocarcinomas (e-CCA).

In cases in which a pathological tissue code was available according to ICD-O-3, we defined adenocarcinomas as shown in Supplementary Table I, based on the World Health Organization International Histological Classification of Tumors and the International Agency for Research on Cancer and Rare Care Net Information Network on Rare Cancers.

Regarding the age of onset, young-onset was defined in cases younger than 65 years of age at the time of diagnosis, while old-onset was defined as 65 years or older.

Because of a broad diversity of direct causes of death from cholangiocarcinoma, overall death was chosen for calculating hazard ratios (HR).

Statistical analysis

A χ square test was performed for differences between percentages of baseline characteristics. The five-year survival rate was estimated using the Kaplan–Meier method. Cox proportional hazard models were used to calculate adjusted HR for overall death. P values < 0.05 or < 0.01 were considered to be statistically significant. Analyses were performed using STATA/MP14.0 software (Stata-Corp LP, College Station, TX).

This study was approved by the Ethics Committee of the University of Tokyo (No. 10891), and the Japan Organization of Occupational Health and Safety, Kanto Rosai Hospital (No. 2014-34).

RESULTS

The total number of patients with gastrointestinal cancer registered in the Kanagawa Prefecture Regional Cancer Registry from 1954 to 2013 was 498,983. Of these, patients with cholangiocarcinoma comprised 14,287 cases from 1976 to 2013. The details are as follows: the numbers of intrahepatic cholangiocarcinoma (C221), extrahepatic cholangiocarcinoma (C240), and carcinoma of the ampulla of Vater (C241) cases were 3,369 (23.6%), 9,285 (65.0%), and 1,633 (11.4%), respectively (Table I).

The numbers of males and females were 8,345 (58.4%) and 5,942 (41.6%), respectively. Cases of i-CCA and e-CCA comprised 3,369 (23.6%) and 10,918 (76.4%), respectively. In Period 1, 10,041 (70.3%) cases were included, while in Period 2, 4,246 (29.7%) cases were recognized (Table I). The average age of patients with cholangiocarcinoma was 71.4 years (± 11.5), and the average age at death was 72.8 years (± 11.4). Data concerning the presence/absence of treatment, except for surgical procedures, was available in 10,837 cases.

Table I. Baseline characteristics of cholangiocarcinoma patients

	Overall†	ICD10			Location of cholangiocarcinoma	
		C221	C240	C241	Intrahepatic	Extrahepatic
Number (%)	14287 (100)	3369 (23.6)	9285 (65.0)	1633 (11.4)	3369 (23.6)	10918 (76.4)
Age at diagnosis, years						
(Mean±SD)‡, years	71.4±11.5	69.6±11.4	72.4±11.4	69.0±11.2	69.6±11.4	71.9±11.4
Age at death						
(Mean±SD)‡	72.8±11.4	70.6±11.4	73.8±11.3	72.0±11.7	70.6±11.4	73.5±11.3
Median of OS¶	185	142	183	402	142	201
IQR (25%:75%)	(62:475)	(54:359)	(61:462)	(137:939)	(65:520)	(54:359)
Gender						
Male	8345 (58.4)	2028 (60.2)	5344 (57.6)	973 (59.6)	2028 (60.2)	6317 (57.9)
Female	5942 (41.6)	1341 (39.8)	3941 (42.4)	660 (40.4)	1341 (39.8)	4601 (42.1)
Period§						
Period 1	10041 (70.3)	2355 (69.9)	6621 (71.3)	1065 (65.2)	2355 (69.9)	7686 (70.4)
Period 2	4246 (29.7)	1014 (30.1)	2664 (28.7)	568 (34.8)	1014 (30.1)	3232 (29.6)
Operation						
Yes	5911 (41.4)	964 (28.6)	3852 (41.5)	1095 (67.1)	964 (28.6)	4947 (45.3)
No	8376 (58.6)	2405 (71.4)	5433 (58.5)	538 (33.0)	2405 (71.4)	5971 (54.7)
Other treatment						
Data available	10837 (75.9)	2583 (76.7)	6815 (73.4)	1429 (87.5)	2593 (77.0)	8244 (75.5)
Chemotherapy¶¶	2288 (21.1)	797 (30.9)	1276 (18.7)	215 (15.0)	797 (30.7)	1491 (18.0)
Radiation¶¶	493 (4.5)	151 (5.8)	327 (4.8)	15 (1.0)	151 (5.8)	342 (4.1)

†Data for 14,287 patients with complete information on sex, age, location of bile duct cancer, and period; ‡SD: Standard deviation.§Period: Period 1: 1976–2005, Period 2: 2006–2013; ¶ Median of OS: median of overall survival (days), IQR: Interquartile range; ¶¶The percentage of cases for whom chemotherapy or radiation was performed to cases with treatment data available.

Three-year survival rate

Figure 1 shows the temporal change in the three-year survival rate (every two years from 1976 to 2013). According to the data, the prognosis of patients appeared to improve with the introduction of new chemotherapeutic agents: the prognosis in 2009–2010 was 40.9%, significantly different from that in 2005–2006 (23.7%), and 2007–2008 (28.4%).

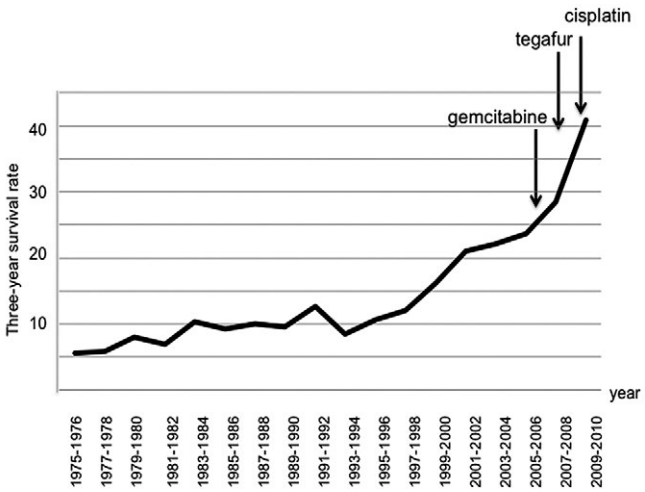

Fig. 1. Three-year survival rates were calculated every two years from 1976 to 2013. Arrows indicate the introduction of gemcitabine, tegafur, and cisplatin treatments.

Figure 2 shows five-year survival rates of i-CCA and e-CCA cases by period. The five-year survival rate of patients with i-CCA was higher in Period 2 (20.3%) than in Period 1 (5.5%), while that of patients with e-CCA also increased from Period 1 (8.7%) to Period 2 (29.4%). For both periods, the survival rate of patients with i-CCA was significantly lower than that of patients with e-CCA ($p < 0.01$). The same trend was observed in analysis after the exclusion of cases with papillary cancer (C241).

Pathology

The number of cases in which pathological tissue was classified based on ICD-O-3 was 5,441. The distribution of patient characteristics in these cases is shown in Table II. Overall, comparing i-CCA and e-CCA cases, a significant difference was observed in the age of onset and whether patients underwent surgery; those patients with i-CCA were more likely to have young-onset ($p < 0.01$) and less likely to have undergone surgery than those with e-CAA ($p < 0.01$). Regarding overall histopathological results, the proportion of non-adenocarcinoma cases was significantly higher in i-CCA than in e-CAA ($p < 0.02$); however, this statistical difference disappeared when we examined the two periods separately. The details of non-adenocarcinoma cases in i-CCA were as follows: 10 patients with squamous cell carcinoma, 6 with undifferentiated, 6 with sarcoma, and 5 with neuroendocrine carcinoma, as well as 3 other cases. Among extrahepatic cholangiocarcinoma cases

Table II. Distribution of cholangiocarcinoma with pathological information

Characteristics Number (%)	Intrahepatic cholangiocarcinoma	Extrahepatic cholangiocarcinoma	P-value‡
Overall (N=5441)			
Gender			0,74
Male	894 (63.6)	2546 (63.1)	
Female	512 (36.4)	1489 (36.9)	
Age of onset†			<0.01**
Old	870 (61.9)	2784 (69.0)	
Young	536 (38.1)	1251 (31.1)	
Pathology			<0.02*
Adenocarcinoma	1376 (97.9)	3985 (98.8)	
Non-adenocarcinoma	30 (2.1)	50 (1.2)	
Operation			<0.01**
Yes	577 (41.0)	2594 (64.3)	
No	829 (58.9)	1441 (35.7)	
Period 1 (N=3088)			
Gender			0.32
Male	546 (62.6)	1345 (60.7)	
Female	326 (37.4)	871 (39.3)	
Age of onset			0.02*
Old	507 (58.0)	1389 (62.7)	
Young	365 (41.9)	827 (37.3)	
Pathology			0.12
Adenocarcinoma	855 (98.0)	2189 (98.8)	
Non-adenocarcinoma	17 (1.2)	27 (1.2)	
Operation			<0.01**
Yes	367 (42.1)	1529 (69.0)	
No	505 (57.9)	687 (31.0)	
Period 2 (N=2353)			
Gender			0.67
Male	348 (65.2)	1201 (66.0)	
Female	186 (34.8)	618 (34.0)	
Age of onset			<0.01**
Old	363 (68.0)	1395 (76.7)	
Young	171 (32.0)	424 (23.3)	
Pathology			0.05
Adenocarcinoma	521 (97.6)	1796 (98.7)	
Non-adenocarcinoma	13 (2.4)	23 (1.3)	
Operation			<0.01**
Yes	210 (39.3)	1065 (58.6)	
No	324 (60.7)	754 (41.5)	

†Young-onset cholangiocarcinoma is defined as patients under 65 years of age; ‡P-value <0.05* or <0.01** were considered to be statistically significant.

there were 17 patients with squamous cell carcinoma, 12 with neuroendocrine carcinoma, 7 with small cell carcinoma, 5 with sarcoma, 5 with a carcinoid tumor, and one undifferentiated, as well as 3 other cases, respectively. There was no significant difference in the distribution of gender between i-CCA and e-CCA cases.

Table III shows HRs adjusted for other factors, including Periods 1 or 2, age of onset, gender, location of the cholangiocarcinoma, histopathology, and whether surgery was performed. In model 1, HRs were analyzed using 5,361 adenocarcinoma cases only. The HR for i-CCA cases was significantly higher than that for e-CCA cases (HR 1.39,

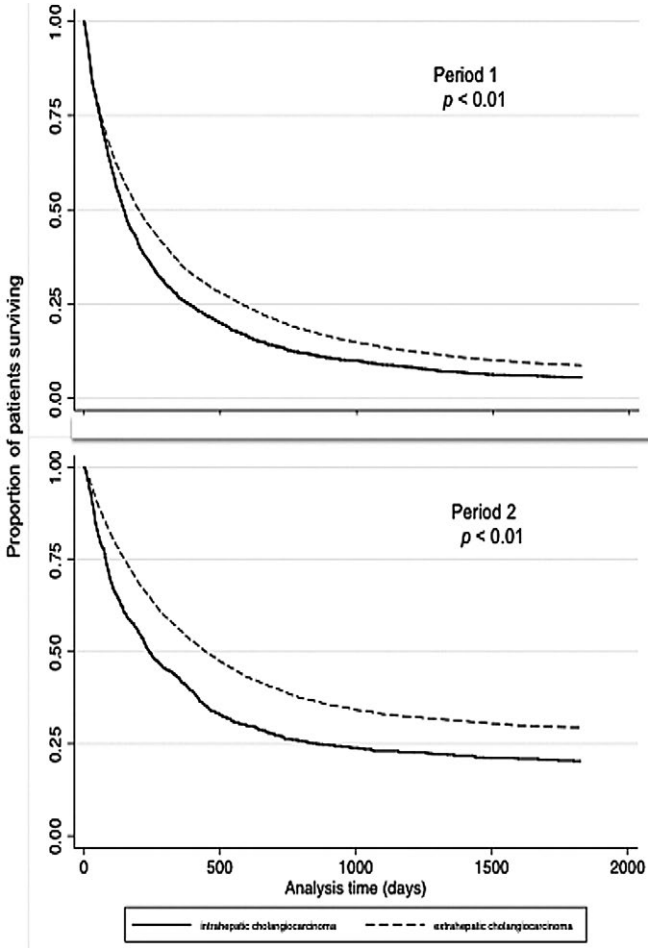

Fig. 2. Kaplan–Meier survival curves for overall survival between intrahepatic and extrahepatic cholangiocarcinoma cases in each period. Survival was estimated using the Kaplan–Meier method in patients with complete information on sex, age, location of bile duct cancer, and observation period, and with right censoring at the 5-year mark. P values were calculated from log-rank tests. With advances in chemotherapy, the survival rate improved for both intrahepatic and extrahepatic cholangiocarcinomas.

95% CI 1.30–1.50). The HR for cases who had undergone surgery was significantly lower than that for those who had not undergone an operation (HR 0.52, 95% CI 0.49–0.56). Model 2 shows HRs analyzed using 5,441 cases, including non-adenocarcinoma. When non-adenocarcinoma cases were included, the p values of each variable did not change. The HR for non-adenocarcinoma cases was significantly lower than that for adenocarcinoma cases (HR 0.71, 95% CI 0.54–0.95).

DISCUSSION

Our study showed that the prognosis of cholangiocarcinoma markedly improved with the introduction of new chemotherapeutic agents. The prognosis was significantly different depending on tumor site and pathological tissue type.

In recent years, cholangiocarcinomas have been classified as intrahepatic, peri-hilar and distal [12, 16, 17]. However, reports concerning the outcome of treatment with anticancer drugs for these three types of cholangiocarcinoma are limited [18-20]. Five-year survival rates were found to be 20–32%, 30–42%, and 18–54% for intrahepatic, hilar, and distal cholangiocarcinomas, respectively [20-31]. The prognostic factors of resected cases are the presence of lymph node metastasis [23, 25, 28] or minute vascular invasion [16]. However, complete resection and adjuvant chemotherapy have improved the prognosis for all tumor sites [19, 20].

A couple of factors have made the clinico-epidemiological analysis of cholangiocarcinoma difficult. The first is the ambiguity in classifying tumor location, the topology of which was changed when moving from the second edition of the International Classification of Diseases for Oncology (ICD-O-2) to its third edition (ICD-O-3). Studying 3,350 cholangiocarcinoma cases between 1992 and 2000, Welzel et al. highlighted the misclassification between intrahepatic and extrahepatic cholangiocarcinoma in the SEER program [32]. In addition, it is often difficult to detect the original site of the tumor if the tumor stage is advanced on initial presentation [16, 32].

Using a large-scale cancer registry, we found that the survival rate of patients with cholangiocarcinoma markedly improved with the introduction of new chemotherapeutic agents. This indicated that the new chemotherapies immediately became popular in Japan and influenced the prognosis of such patients. Regarding the location of the tumor, i-CCA cases had a poorer prognosis than e-CCA throughout the entire period studied. This difference was noted both before and after the introduction of a new type of chemotherapy, probably due to the characteristics of the disease itself. In the case of patients with e-CCA, the presence of obstructive jaundice accelerates the diagnosis of this disease. In contrast, in patients with i-CCA, the disease progresses without any signs and symptoms resulting in a delay in its diagnosis [7]. The reasons for the difference in the prognosis between i-CCA and e-CCA cases may also originate from the type of surgery performed. In i-CCA cases, hepatectomy is generally undertaken and therefore residual liver function becomes an important prognostic factor [33]. In e-CCA cases, pancreatoduodenectomy is mostly indicated. If this procedure is successfully carried out, the resulting prognosis may be favorable [15, 34]. Therefore, differences in the type of surgery undertaken may have also caused the difference observed in the prognosis of patients with the two types of cholangiocarcinomas.

It is also true that no clear evidence exists that chemotherapy confers any survival benefit to patients with all histologic subtypes of cholangiocarcinoma, because the number of variant cases is not substantial enough to undertake a meaningful statistical analysis [24, 35, 36]. Moreover, large-scale epidemiological studies do not exist with regard to differences in prognosis that may occur among cholangiocarcinoma cases with different histopathological aspects. Cholangiocarcinoma mostly consists of adenocarcinoma and a few other variants [37]. In this study, histopathological information was obtained for 5,441 cases, about one-third of the total cholangiocarcinoma cases studied. As we have previously reported, the proportions of young-onset and non-adenocarcinoma cases were significantly higher for i-CCA [38, 39]. The current study also showed the same tendency. In addition, this study suggested that the prognosis for patients with adenocarcinoma was poorer than that for patients with non-adenocarcinoma.

Table III. Hazard ratios for overall deaths adjusted for available confounders

	Hazard ratio (95% CI)†		Hazard ratio (95% CI)†	
Characteristics	Model 1 (n=5361)	P-value§	Model 2 (n=5441)	P-value§
Period‡				
Period 1	1.00 (ref)		1.00 (ref)	
Period 2	0.49 (0.46-0.53)	<0.01**	0.49 (0.46-0.52)	<0.01**
Age of onset				
Old	1.00 (ref)		1.00 (ref)	
Young	0.87 (0.82-0.94)	<0.01**	0.87 (0.81-0.93)	<0.01**
Gender				
Male	1.00 (ref)		1.00 (ref)	
Female	1.02 (0.96-1.09)	0.41	1.02 (0.96-1.09)	0.43
Location of cholangiocarcinoma				
Extrahepatic	1.00 (ref)		1.00 (ref)	
Intrahepatic	1.39 (1.30-1.50)	<0.01**	1.38 (1.29-1.48)	<0.01**
Operation				
No	1.00 (ref)		1.00 (ref)	
Yes	0.52 (0.49-0.56)	<0.01**	0.52 (0.49-0.55)	<0.01**
Pathology				
Adenocarcinoma	-		1.00 (ref)	
Non-adenocarcinoma	-	-	0.71 (0.54-0.95)	<0.02*

†Data analyzed by a Cox proportional hazards model between the variables of observation period, age, gender, location of cholangiocarcinoma, operation and pathology. Model 1 was analyzed using 5361 cases with adenocarcinoma only. Model 2 involved 5441 patients that included non-adenocarcinoma cases. ‡Period: Period 1: 1976–2005, Period 2: 2006–2013; §P-value <0.05* or <0.01** was considered to be statistically significant.

Since, for these analysis periods, chemotherapy may be the only difference in treatment strategies among adenocarcinoma and non-adenocarcinoma cases, adenocarcinoma may have been more strongly resistant to chemotherapy.

As for cholangiocarcinoma, obtaining pathological tissue is difficult as it is only available after surgery is performed. In many cases, cytology by endoscopic retrograde cholangiopancreatography (ERCP) is used for a diagnosis. Unfortunately, an ERCP cytodiagnosis often yields ambiguous results since it is mainly performed for the quick, rapid relief and suppression of infection and jaundice [15, 40]. However, since the effectiveness of anti-cancer drugs depends on the histological nature of the disease, a pathological diagnosis is very important as shown in the current study. In addition, early diagnosis is required since non-adenocarcinomas, such as neuroendocrine tumors, may already be at an advanced stage at the time of diagnosis [35, 41].

Reasons why the age at onset as well as pathological tissue differed between i-CCA and e-CCA are considered as follows: known risk factors for cholangiocarcinoma include intrahepatic stones, liver fluke, biliary-duct cysts, and toxins. Differences in such risk factors between i-CCA and e-CCA may exist [42]. In addition to these environmental factors, host factors also influence carcinogenesis. The intrahepatic bile duct consists of cells of different origin, including cuboidal non–mucin-producing cholangiocytes, mucin-producing cholangiocytes and hepatic progenitor cells (HPCs) [43]. An i-CCA grows from such heterogeneous cells. The histological appearance is not uniform: a mixed type is seen in the small intrahepatic bile duct and a mucinous type is seen in the large intrahepatic bile duct [33, 44, 45]. In contrast, e-CCA originates from a single cell, and therefore tends to consist of a single mucinous adenocarcinoma [44].

In Japan, gemcitabine has been used as a standard chemotherapy for unresectable cholangiocarcinoma since 2006 while tegafur/gimeracil was approved in 2008. Although cisplatin was approved in 2011, it does not appear effective enough to bring on a radical cure [8]. Despite the rise in morbidity due to an aging population, the survival rate for patients with cholangiocarcinoma has clearly improved with the increasing availability of chemotherapy [33]. Additionally, continuous advances in surgical techniques and drainage technology for cholangitis have contributed to a better prognosis for cholangiocarcinoma. Overall, combined therapies using new techniques such as cholangiopancreatoscopy is expected to improve treatment and further enhance the prognosis of patients with cholangiocarcinoma.

TNM classifications were available for 1,902 cases and we calculated the HR for overall death after including this information. We defined cases in stages 1–3 as a reference. The HRs for the period, young-onset/old-onset, site of tumor, gender, adenocarcinoma/non-adenocarcinoma, operation, and TNM staging were 0.71 (95% CI 0.54–0.96), 0.84 (95% CI 0.73–0.91), 1.39 (95% CI 1.22–1.59), 1.00 (95% CI 0.86–1.13), 0.40 (95% CI 0.20–0.80), 0.67 (95% CI 0.59–0.76) and 3.01 (95% CI 2.63–3.44), respectively. Even though we included information on TNM, our main results were only slightly affected.

Several limitations exist in this study. Firstly, with regard to selection bias, differences in mortality among sub-groups may exist. However, because DCO cases in this study were 18.2%, which was less than the 20% reliability criterion of the cancer registry, this suggested that the precision of the overall survival estimates was high and that selection bias was minimal. Secondly, because of the nature of the database, we could not adjust for factors that were common risk factors for cholangiocarcinoma (viral hepatitis, primary sclerosing cholangitis, hepatolithiasis, smoking, occupation, and socioeconomic conditions) and therefore these factors may have been confounding with regard to the findings of the current study. Thirdly, little information on treatments existed. For example, we did not have detailed information about operation methods or chemotherapy regimens; therefore, we could not identify which therapies actually improved the prognosis of i-CCA and e-CCA cases after 2006. Such pivotal information should be collected in any future studies.

CONCLUSION

This study revealed two important findings. First, we found an obvious difference in prognosis between patients with intrahepatic or extrahepatic cholangiocarcinoma. Second, non-adenocarcinoma cases showed a better survival rate than adenocarcinoma cases. These results will be helpful in any future research and treatment of cholangiocarcinoma.

Conflicts of interest: The authors declare that they have no conflict of interest.

Authors' contribution: R.K. collected and analyzed the data, and drafted the manuscript; Y.S. contributed to the study design; Y.K. supervised the study. All the authors read and approved the final version to be published.

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Supplementary table I. Definition of cholangiocarcinoma pathologies.

Characteristics	Definition by ICD-O-3
adenocarcinoma[†]	Intrahepatic Bile Tract 8160,8140–8141, 8143,8147,8162,8190,8201,8210–8211 8221,8230–8231,8255,8260–8263,8290,8310,8315,8320 8323,8333,8380–8384,8430,8440–8441,8450,8480–8482 8490,8500,8503–8504,8510,8512,8514,8525,8542 8550–8551,8560,8562,8571–8576 Extra Bile Tract 8020–8022,8050,8140–8141,8143,8144,8147,8160,8162 8190,8200,8201,8210–8211,8221,8230–8231,8251,8255 8260–8263,8290,8310,8315,8320,8323,8333,8350, 8380–8384,8430,8440–8441,8450,8480,8482,8490 8500,8503–8504,8510,8512,8514,8521,8525,8542,8550 8551,8560–8562,8570,8571–8576

[†]Adenocarcinoma of the bile duct using Information Network on Rare Cancers RARECARENet.

RESEARCH ARTICLE

The Effect of New Therapeutic and Diagnostic Agents on the Prognosis of Hepatocellular Carcinoma in Japan – An Analysis of Data from the Kanagawa Cancer Registry

Rena Kaneko*, Natsuko Nakazaki, Risa Omori, Yuichiro Yano, Masazumi Ogawa, Yuzuru Sato

Abstract

Objective: Notable advances in diagnostic imaging modalities and therapeutic agents have contributed to improvement in the prognosis of hepatocellular carcinoma (HCC) over the past decade. However, knowledge concerning their epidemiological contribution remains limited. The present study investigated the effect of emerging diagnostic and therapeutic agents on HCC prognosis, using the largest regional cancer registry in Japan. **Methods:** Using data from the Kanagawa Cancer Registry, the five-year survival rate of patients with liver cancer was estimated according to the International Statistical Classification of Diseases and Related Health Problems (10th Edition). **Result:** A total of 40,276 cases of HCC (from 1976 to 2013) were identified. The prognosis markedly improved after the introduction of new devices into the diagnosis and treatment of HCC ($p<0.01$). The trend of survival rate varied significantly between institutions with many registered patients (high-volume centers) ($p<0.01$). **Conclusion:** The five-year survival rate of patients with HCC in Kanagawa has markedly improved in recent years. This improvement in survival may be attributed to the advances in surveillance and intervention for the treatment of HCC.

Keywords: liver cancer- hepatocellular carcinoma- survival- epidemiology

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Introduction

Hepatocellular carcinoma (HCC) is the sixth most common cancer worldwide and the fourth most common in Japan (Umemura et al., 2009; Zhu et al., 2016).

Treatment options are limited, with guidelines recommending resection, ablation, chemoembolization, radiotherapy or chemotherapy, depending on liver function and tumor burden (Makuuchi and Kokudo, 2006; Bruix and Sherman, 2011; Kudo et al., 2011). Detection of the tumor at an early stage of disease, coupled with effective systemic therapy, improves long-term survival in patients with HCC. (Forner et al., 2008)

In Japan, radiofrequency ablation (RFA) was approved in 2004 as a new curative treatment of HCC. In 2007, a new contrast-enhanced ultrasound agent known as perfluorobutane was approved. During the same year, gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid (Gd-EOB-DTPA) used in magnetic resonance imaging (MRI) was also approved. In 2009, sorafenib – an oral multikinase inhibitor – was introduced in the treatment of advanced HCC.

Although these new treatment and diagnosis options have become available, there is a lack of evidence from randomized controlled trials addressing their impact on HCC incidence and management. This may be due to the tailored treatment required to address the disease characteristics of HCC (Best et al., 2017).

The objective of this study was to examine the epidemiological effect of these new agents on the prognosis of HCC, using a large-scale cancer registry in Japan.

Materials and Methods

Kanagawa Cancer Registry

The Kanagawa Prefecture is the second largest in Japan, with a population of approximately nine million people. The Kanagawa Cancer Registry was founded in 1954, and is the largest regional cancer registry in Japan. By the end of 2013, the registry had accumulated and recorded approximately 990,000 cancer cases in the region. Details on the cancer registry system in Japan have been discussed elsewhere (Okamoto, 2008). Data were collected from neoplasm registration sheets produced by the diagnosing hospitals or from clinic and death certificates of patients residing in the Kanagawa Prefecture. The Kanagawa Cancer Center collected and

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consolidated the data into an anonymous format (to protect the identity of patients), making them available for research purposes.

The accumulated data include the following information: 1) personal identification code, 2) method of registry entry, 3) diagnosing institution, 4) sex, 5) date of birth, 6) date of diagnosis, 7) local government code for the patient's home address, 8) ICD-10 code for disease name, 9) ICD-O-3 code for pathology, 10) initial or recurrent tumor state, 11) therapeutic strategy (very brief), 12) operative procedure (if any), 13) date of death, 14) cause of death, 15) date of last follow-up and 16) tumor/node/metastasis (TNM) classification and pathological grade according to ICD-O-3 in diagnosed patients. The reporting of TNM classifications became mandatory in 2005.

All information was collected by trained healthcare professionals in Japan according to the Surveillance, Epidemiology, and End Results (SEER) program. Information was updated every year from vital statistics and death certificates. Previous versions of pathological codes were updated to the latest versions through standardized regulations consistent with changes in coding practices for cholangiocarcinoma. The proportion of death-certificate-only (DCO) cases in the entire database was 18.2% by the end of 2013 (Goverment, 2016).

Subjects and classification method

Clinical data relating to gastrointestinal cancers between June 15, 1954 and December 30, 2013 were obtained from the Kanagawa Cancer Center. From these records, data pertaining to liver cancer (C220), according to the International Statistical Classification of Diseases and Related Health Problems (ICD), 10th Revision (ICD-10), were extracted and included for analysis in the present study.

In order to estimate the five-year survival rate of patients, the analysis period was divided into four parts: (1) from 1954 to 1999 (4 years prior to the introduction of RFA), (2) from 2000 to 2003 (4 years prior to RFA approval), (3) from 2004 to 2007 (from RFA administration until Gd-EOB-DTPA and perfluorobutane approval) and (4) from 2008 to 2013 (following the approval of Gd-EOB-DTPA, perfluorobutane and sorafenib). Due to the one-year difference in the approvals of Gd-EOB-DTPA, perfluorobutane and sorafenib, the last period was analyzed collectively.

The two-year survival rate of patients every two years was calculated, to determine the trend in patient survival rate throughout the entire analysis period.

The analysis was limited to high-volume centers (facilities registering >400 cases) and cases with available TNM classification. The differences in the survival rates between these facilities were also estimated. Each high-volume center was assigned a letter (from A to O), according to the five-year survival rate ranking.

Statistical analysis

The five-year survival rate was estimated using the Kaplan–Meier method. P values <0.05*or <0.01** were considered to be statistically significant. Analyses were performed using the STATA/MP14.0 software (Stata-Corp LP, College Station, TX).

This study was approved by the ethics committee of the Japan Organization of Occupational Health and Safety Kanto Rosai Hospital (No.2014-34).

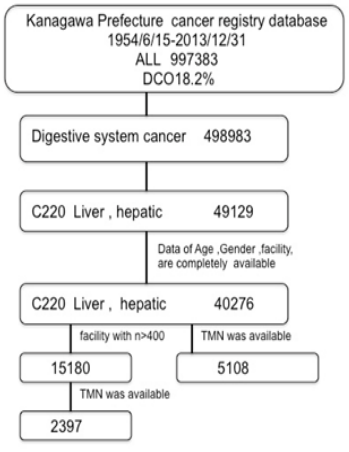

Figure 1. Flow Diagram of Patient Selection Out of a Total of 997,383 Patients (from 1954 to 2013) Identified in the Database of the Kanagawa Cancer Registry, to Reach the Final Number of Eligible Patients Included in This Survival Analysis.

Results

The total number of patients with gastrointestinal cancer registered in the Kanagawa Cancer Registry from 1954 to 2013 was 498,983. Among them, patients with HCC comprised 49,129 cases registered between 1976 and 2013. Of those, 40,276 cases with complete data were enrolled in the present study. Of note, the records of 15,180 cases were derived from the top 15 high-volume centers. The number of cases with available TNM classification was 5,108 (Figure 1).

The average age of patients with HCC was 66.6 years (±10.7), and their average age at death was 68.3 years (±10.8). Approximately three-quarters of patients were males (29,646; 73.6%), whereas 10,630 (26.4%) were

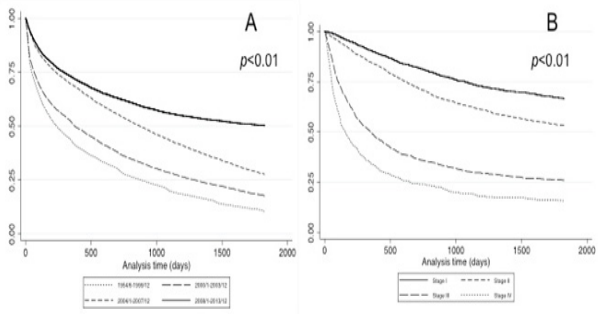

Figure 2. Kaplan–Meier Survival Curves for Overall Survival in Each Period (A) and TNM Stage (B) for Patients with Hepatocellular Carcinoma. Survival was estimated using the Kaplan–Meier method in 31,921 patients with complete information on sex, age and observation period, and with right censoring at the 5-year mark. The p values were calculated using a log-rank test. TNM, tumor/node/metastasis classification

Table 1. Baseline Characteristics

Period	N (%)[2]	Age of diagnosis (mean±SD)	Age of death (mean±SD)	Gender	
				Male (%)	Female (%)
Overall[1]	4,0276 (100)	66.6±10.7	68.31±10.79	29,646 (73.6)	10,630 (26.39)
1954-1999	22,968 (57.0)	64.2±10.5	66.0±10.6	17,435 (75.9)	5,523 (24.1)
2000-2003	6,161 (15.3)	68.8±9.8	71.0±9.8	4,442 (72.1)	1,790 (27.9)
2004-2007[3]	4,546 (11.3)	69.5±9.6	72.5±9.5	3,191 (70.2)	1,355 (29.8)
2008-2013[4]	6,611 (16.3)	71.3±10.4	73.8±10.1	4,578 (69.3)	2,033 (30.8)

[1]Data for 40,276 patients with complete information on sex, age and period; [2]Because of rounding, percentages may not total 100; [3]Period after radiofrequency ablation was approved for the treatment; [4]Period after Gd-EOB, Perflubutane and Sorafenib was approved for the treatment.

Table 2. Distribution of TMN Stage in Each Period

Period	N (%)[1]	TMN[5] stage at initial daignosis			
		1	2	3	4
Overall[1]	5108	1,849 (36.2)	1,635 (32.0)	1,111 (21.8)	513 (10.4)
1954-1999	25	6 (24.0)	11 (44.0)	7 (28.0)	1 (4.0)
2000-2003	91	25 (27.5)	31 (34.1)	21 (23.1)	14 (15.4)
2004-2007[3]	820	246 (30.0)	269 (32.8)	201 (24.5)	104 (12.7)
2008-2013[4]	4172	1,572 (37.7)	1,324 (31.8)	882 (21.1)	394 (9.4)

[1]Data for 5108 patients with complete information on sex, age, period and TMN stage; [2]Because of rounding, percentages may not total 100; [3]Period after radiofrequency ablation was approved for the treatment; [4]Period after Gd-EOB, Perflubutane and Sorafenib was approved for the treatment; [5]TNM, tumor/node/metastasis classification.

females. Cases of HCC, classified according to study period were: 22,968 (57.0%), 6,161 (15.3%), 4,546 (11.3%) and 6,611 (16.3%), for the study parts 1954-1999, 2000-2003, 2004-2007 and 2008-2013, respectively (Table 1).

The distribution of disease stage at initial registration for the 5,108 cases with available TNM classification is demonstrated in Table 2. The proportion of stage I disease gradually increased over time: 24% (1954-1999), 27.5% (2000-2003), 30% (2004-2007) and 37.7% (2008-2013).

Five-year survival rate

Figure 2 shows five-year survival rates prior to and after the introduction of new diagnostic and therapeutic modalities (A) and by TNM classification (B). Based on the data, the five-year survival rate was prolonged over time: 10.4% (1954-1999), 17.5% (2000-2003), 27.6% (2004-2007) and 50.2% (2008-2013) ($p<0.01$). TNM classification demonstrated the following: 66.7% (stage I), 55.3% (stage II), 25.9% (stage III) and 15.7% (stage IV) respectively ($p<0.01$).

Figure 3 shows the temporal change in the two-year survival rate (every two years from 1975 to 2013). According to the data, prognosis was improved with the introduction of new diagnostic and therapeutic agents.

Five-year survival rate in high-volume centers

Fifteen institutions were identified as high-volume centers. The five-year survival rate was estimated for each facility. Figures 4A and 4B show survival rates for all cases and for those who underwent surgical resection, respectively. The performance ranking among facilities remained unchanged regardless of surgical treatment. The survival rate of facility A was 49.8% in all cases and 47.6% in those who underwent surgery. In contrast, the

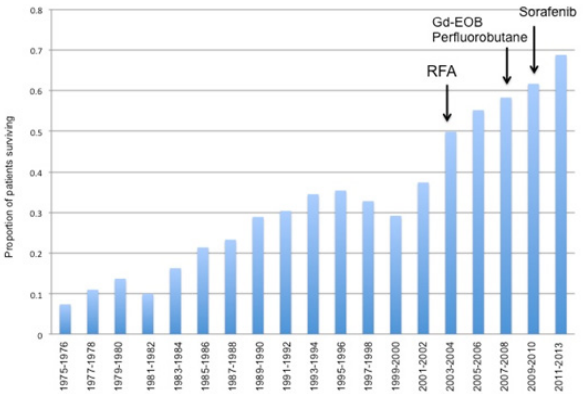

Figure 3. Two-Year Survival Rate Every Two Years from 1975 to 2013. Arrows show the time of radiofrequency ablation, Gd-EOB-DTPA, perfluorobutane and sorafenib introduction. RFA, radiofrequency ablation; Gd-EOB-DTPA, gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid

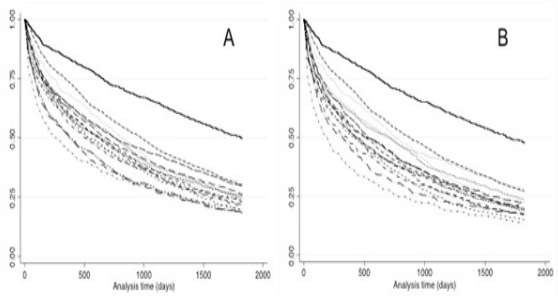

Figure 4. Five-Year Survival Estimated for All High-Volume Centers. Kaplan–Meier survival curves for the overall survival of patients with hepatocellular carcinoma in all cases (A) and those who underwent surgery (B).

Table 3. Distribution of TMN Staging in Each Hospital Over 400 Registered Cases

Rank	Hospital	N (%)		TMN[1] staging at initial daignosis			
		Overall	Stage available	1	2	3	4
1	A	615	235	55 (25.4)	107 (45.5)	46 (19.6)	27 (11.5)
2	B	1,624	100	22 (22.0)	49 (49.0)	20 (20)	9 (9)
3	C	890	6	2 (33.3)	2 (33.3)	1 (16.7)	1 (16.7)
4	D	1,467	338	160 (47)	107 (31.7)	55 (16.3)	16 (4.7)
5	E	639	154	58 (37.7)	36 (23.4)	20 (13.0)	40 (26.0)
6	F	1132	185	47 (25.4)	64 (34.6)	48 (26.0)	26 (14.1)
7	G	566	9	2 (22.2)	2 (22.2)	4 (44.4)	1 (11.1)
8	H	707	215	97 (45.1)	61 (28.4)	46 (21.4)	11 (5.1)
9	I	1,074	460	189 (41.1)	127 (27.6)	121 (26.3)	23 (5)
10	J	616	78	37 (47.4)	23 (29.5)	11 (14.1)	7 (9.0)
11	K	1,033	312	116 (37.2)	116 (37.2)	57 (18.3)	23 (7.4)
12	L	676	128	45 (35.2)	43 (33.6)	31 (24.2)	9 (7.0)
13	M	509	25	4 (16.0)	9 (36.0)	8 (32.0)	4 (16.0)
14	N	400	95	25 (26.3)	20 (21.1)	29 (30.5)	21 (22.1)
15	O	489	57	12 (21.1)	23 (40.4)	19 (33.3)	3 (5.3)

[1]TNM, tumor/node/metastasis classification

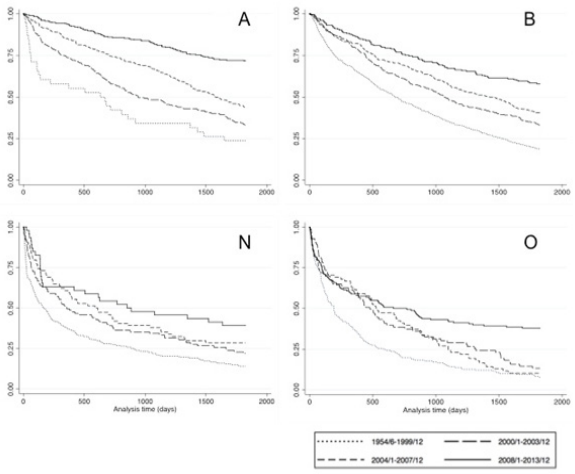

Figure 5. Temporal Change in Five-Year Survival in the Facilities with the Highest Prognosis (A and B), and in Those Two with the Lowest prognosis (N and O). A consistent improvement was obtained in facilities A and B, unlike facilities N and O in which improvement was inconsistent.

rate of facility O was 18.6% and 13.7%, respectively.

Figure 5 demonstrates temporal changes in the five-year survival rate observed in the two facilities with the highest rates (A and B) and the two facilities with the lowest rates (N and O). During the four analysis periods, prognosis improved in facility A (23.7%, 33.4%, 43.4% and 71.8%) and facility B (18.7%, 32.9%, 40.6% and 58.1%, respectively). In contrast, improvement was low in facility N (14.0%, 22.9%, 28.4% and 39.1%) and facility O (7.7%, 10.3%, 13.3% and 37.9%, respectively).

Table 3 shows HCC staging at initial registration. Facilities A, D, F, H and I were university hospitals and cancer center hospitals. Facilities E and N with the proportion of stage IV cases >20%, and facility M (stage IV >15%) were located in the port and harbor of the prefecture.

Discussion

This study demonstrated that the prognosis of HCC improved over the past four decades, as a result of the introduction of new diagnostic and therapeutic agents. The rate of improvement was significantly different between facilities.

According to the data from a large-scale cancer registry, the five-year survival rate of HCC patients improved consistently over time. The prognosis of HCC was good for all stages of disease (I-IV). These results secure the external validity of this data source.

The Kaplan–Meier curve for the period 2008-2013 reached "plateau" after 1,000 days of analysis time as shown in Figure 2. A reason for this may be that the surviving patients at the end of this analysis were censored. However, the most important reason may be the early diagnosis of cancer enabled by the introduction of new diagnostic modalities and effective treatment options. Detection of the tumor at an early stage, when effective therapy may be applied, is important for achieving long-term survival (Forner et al., 2008). Gd-EOB-DTPA and perfluorobutane permitted the evaluation of early-stage HCC and prolonged survival (Matsuda et al., 2014;Kim et al., 2015). Imaging with Gd-EOB-DTPA presented higher diagnostic accuracy and sensitivity compared with 64-section multidetector computed tomography (CT) (Di Martino et al., 2010;Akai et al., 2011). Perfluorobutane enabled the detection of small HCC visible only through dynamic CT in continuous view, unlike the B-mode (Kan et al., 2010;Mandai et al., 2011). These agents contributed to the detection of early-stage HCC and may be responsible for the observed increase in the proportion of stage I cases (Table 2). Consequently, the two-year survival rate was markedly improved with

the introduction of new diagnostic and therapeutic agents (Figure 3).

Approximately, 70% of HCC cases in Japan are attributable to hepatitis C virus (HCV) infection (Lavanchy, 2011;Zhu et al.,, 2016). The overall reduction in HCC mortality observed since the late 1990s in Japan may be associated with the decreased incidence and improved management of HCV infection compared with the period between 1940 and 1970. During this time, the widespread use of unsterile needles and blood transfusions resulted in an epidemic of HCV infection. (Nishiguchi et al., 1995; Tanaka et al., 2008; Umemura et al., 2009; Goh et al., 2015; Bertuccio et al., 2017). In addition, protease inhibitors such as simeprevir or telaprevir resulting in highly sustained virologic response (SVR) in HCV were introduced in 2013 (Kumada et al., 2012; Hayashi et al., 2014; Izumi et al., 2014). More recently, direct-acting antiviral agents inhibiting key viral functions have become the mainstay of anti-HCV treatment (Pawlotsky, 2013; Suzuki et al., 2013; Mizokami et al., 2015). Prior to the introduction of these therapeutic agents, interferon (IFN)-based treatment was recognized as the standard therapy against HCV infection (Izumi, 2010), despite the suboptimal SVR induced by this treatment (40%-50%). However, patients responding to IFN therapy and sustaining loss of HCV RNA are generally regarded as being at low risk of developing liver cirrhosis or HCC (Nishiguchi et al., 1995). Furthermore, IFN decreased the rate of carcinogenesis in those with normal or persistent low alanine aminotransferase levels (Ikeda et al., 1999). These continuous efforts and advances in anti-HCV therapy may have influenced the improvement in the long-term outcome of patients with HCV.

Sorafenib, an oral multikinase inhibitor with antiproliferative and antiangiogenic effects, was an epoch-making drug for HCC. This agent has been shown to improve overall survival in patients with advanced HCC (Llovet et al., 2008; Cheng et al., 2009). In the past 30 years, the use of anticancer agents for the treatment of HCC has not shown consistent survival benefits (Llovet and Bruix, 2003; Lopez et al., 2006). Sorafenib successfully addressed this unmet medical need, prolonging patient survival. This effect may have contributed to the prolonged five-year survival rate observed after 2009 in this study.

Survival rates varied considerably between the high-volume centers investigated in this study. Prognosis was shown to improve over time in all facilities. However, institutions linked to good prognosis tended to improve more aggressively than those associated with poor prognosis. The reason for this tendency may be "lead-time bias" (Huo et al., 2007; Singal et al., 2014). The detection of early-stage HCC and the appropriate administration of curative treatment leads to prolonged survival (Huo et al., 2007; Oeda et al., 2016; Singal et al., 2017).

It has been shown that the proportion of patients with small-size HCC and curative therapy was higher in the surveillance group than in the non-surveillance group (Tanaka et al., 2006).

Morphological differentiation between early-stage, well-differentiated HCC and dysplastic nodules is often challenging (Kojiro and Roskams, 2005). The approach toward initiating treatment of a small nodule as an early cancer differs among facilities. To address this point, the distribution of cases according to the TNM classification of disease stage was evaluated in this study (Table 3). The results showed that the distribution of staging was affected by locality and did not relate to the ranking based on survival rate. However, the cases with TNM stage were very few and the lead-time bias remained the main reason for this difference.

In addition, the preferred treatment against HCC differs among facilities. The use of methods such as transarterial chemoembolization (TACE) was heterogeneous between facilities, and the timing of administration of a multikinase inhibitor may be critical to the outcome of HCC (Lencioni et al., 2016).

This is the first study to examine the prognosis of HCC over approximately 40 years using a large-scale database. However, the available data did not include information regarding the etiological factors affecting HCC such as liver function, viral infection and treatment course. Therefore, it was not possible to determine the cause of these changes in survival rate.

In conclusion, this study revealed that five-year survival of HCC improved over the past decades. This may be explained by the development of surveillance and follow-up screening for high-risk groups among HCC patients. This allowed the early detection of HCC and appropriate curative intervention, consequently improving patient survival.

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Statement conflict of Interest

The authors declare no conflicts of interest associated with this manuscript.

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神 奈 川 の が ん

（神奈川県と全国の経年比較・研究の紹介）

平成30年3月

神奈川県立がんセンター

診断治療技術の進歩が肝臓癌の予後に与えた影響をがん登録から捉える

関東労災病院　消化器内科　　金子　麗奈

地域がん登録は、長年にわたる日本の癌の軌跡を記した貴重な大規模データベースである。しかし、input の継続的な集積がなされる一方、output の機会が少ないのが現状である。臨床医が癌について考える際、患者の臨床的背景は極めて大事な要素となるが、がん登録には各癌の背景となる臨床情報が含まれていないことも、治療にあたる側からの output がしにくい原因である。では、このデータベースから、我々の日常診療が反映される側面を捉えられないか、を考えた。

そこで、国内の癌死亡の第5位を占める肝臓癌を用い、時代の変遷とともに癌の予後が改善したと言えるのか、また、施設間格差が存在するかをがん登録から検証することとした。

経年ごとの2年生存率に、肝臓癌の診療において epoch making であった経皮的ラジオ波焼灼術(RFA)、経口抗癌剤であるソラフェニブ、早期診断に貢献した Gd－EOB、ペルフルブタンが発売された時期を組み込み、視覚的に予後の改善傾向を捉えることができる図を作成した。

肝細胞癌の治療はガイドラインでスタンダードが決められているものの、施設によって得意とする治療手段が異なるため、肝細胞癌の症例数の多い施設による予後の施設間格差、および、単一施設内での予後改善の動向について、施設ごとに検討した。

2013年末までに神奈川県地域がん登録に登録された初発肝臓癌は40,276例であった。これらのうち、生存期間が解析可能であった症例について、経年による2年生存率を算出したものが図1である。肝予備能の悪い症例の発癌であっても根治を可能にした RFA は、生存率の改善に大きく貢献した可能性が見て取れる。

登録症例数上位15施設の5年生存率を施設ごとに算出したものが図2である。全症例(図2A)でも、手術症例に限っても（図2B)、施設順位に差は認めなかった。これらの施設の生存率上位2施設、下位2施設で、年代による5年生存率の変遷を捉えたものが図3である。上位2施設(A、B)では経年とともに予後が一定の割合で改善しているが、下位2施設(N、O)では改善傾向が乏しいことがわかる。

以上の分析から多くの推測ができる。特筆すべきは、2008年－2013年の症例の生存曲線の末端が水平に達しており（非表示)、肝細胞癌が死因とならなくなったことを示している。診断技術の向上が早期発見を可能にし、治療技術の向上が治療成績を上げた成果であると言えよう。また、神奈川県の肝臓癌の予後は、全体として経年とともに着実に改善していたが、施設間格差があることも判明した。予後が良い施設は、新たな診断治療デバイスを着実に使いこなすことでより効果的に生存期間を延ばしている可能性があり、積極的な新技術の導入と応用が良好な結果につながることが示唆される。しかし、登録情報の欠如から、様々な交絡因子の調整ができず、予測に過ぎない点も多いのが、がん登録の解析の限界である。

2014年以降C型肝炎が容易に根治する時代になり、肝臓癌の絶対数は急激に減少し、予後も劇的に変化していくことが予測される。今後も、がん登録を用いて診療の成果の動向を検討していきたい。

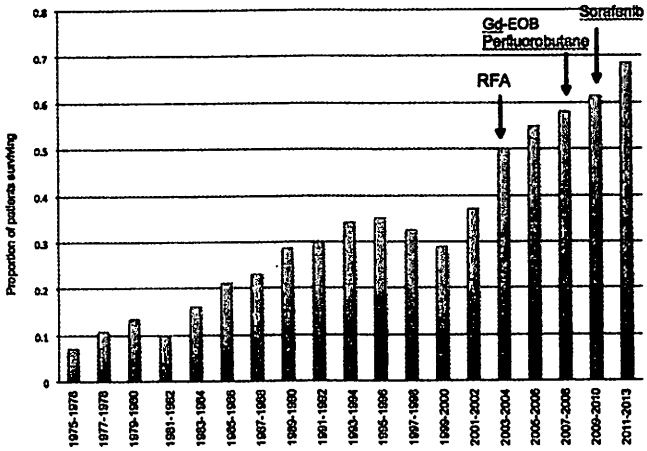

図1　2年ごとの5年生存率

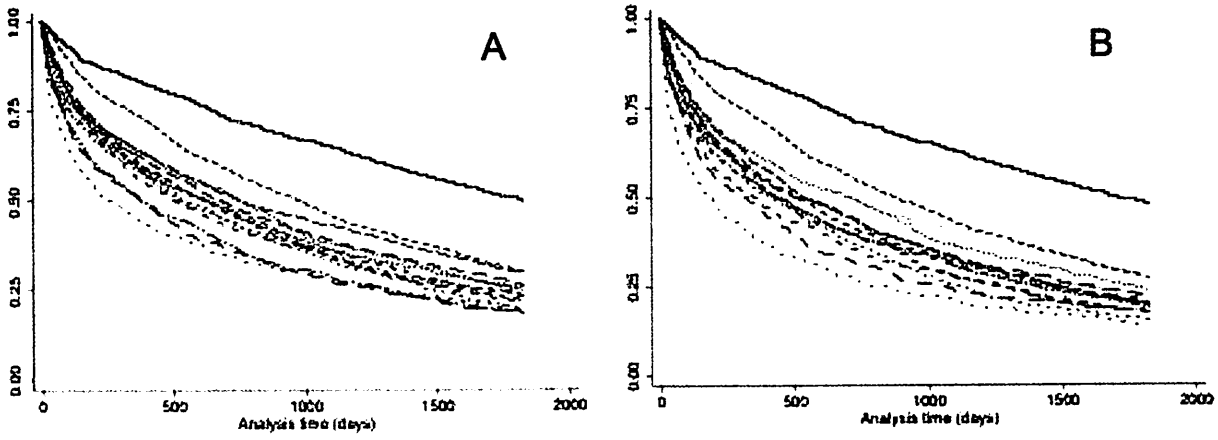

図2　登録数上位施設ごとの5年生存率（A：全症例　B：手術症例）

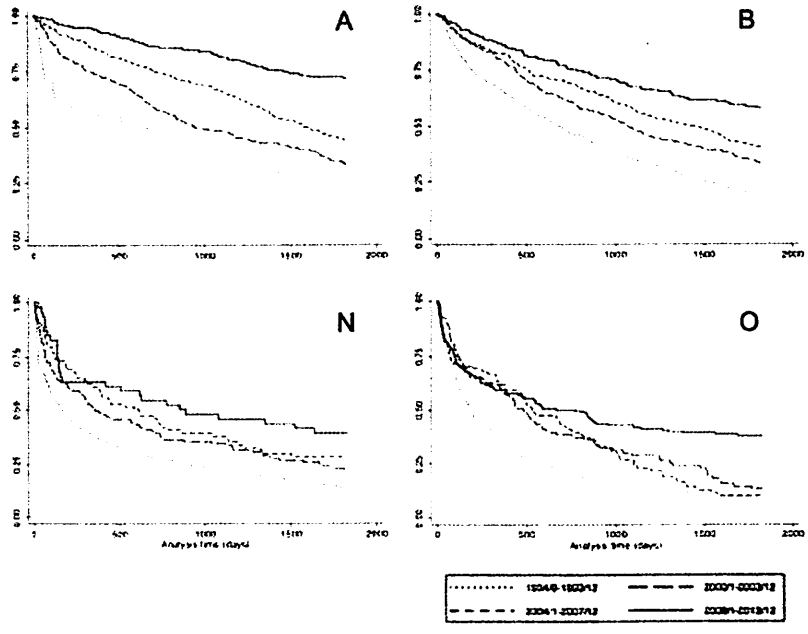

図3 各施設の生存率の経年推移

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Article

Occupational inequalities in female cancer incidence in Japan: Hospital-based matched case-control study with occupational class

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ABSTRACT

Background: Socioeconomic inequalities in female cancer incidence have previously been undocumented in Japan.

Methods: Using a nationwide inpatient dataset (1984–2016) in Japan, we identified 143,806 female cancer cases and 703,157 controls matched for sex, age, admission date, and admitting hospital, and performed a hospital-based matched case-control study. Based on standardized national classification, we categorized patients' socioeconomic status (SES) by occupational class (blue-collar, service, professional, manager), cross-classified by industry sector (blue-collar, service, white-collar). Using blue-collar workers in blue-collar industries as the reference group, we estimated the odds ratio (OR) for each cancer incidence using conditional logistic regression with multiple imputation, adjusted for major modifiable risk factors (smoking, alcohol consumption).

Results: We identified lower risks among higher-SES women for common and overall cancers: e.g., ORs for managers in blue-collar industries were 0.67 (95% confidence interval [CI], 0.46–0.98) for stomach cancer and 0.40 (95% CI, 0.19–0.86) for lung cancer. Higher risks with higher SES were evident for breast cancer: the OR for professionals in service industries was 1.60 (95% CI, 1.29–1.98). With some cancers, homemakers showed a similar trend to subjects with higher SES; however, the magnitude of the OR was weaker than those with higher SES.

Conclusions: Even after controlling for major modifiable risk factors, socioeconomic inequalities were evident for female cancer incidence in Japan.

1. Background

Socioeconomic status (SES), including occupational class, has been recognized as a fundamental social determinant of health, and that also applies to cancer incidence (Krieger et al., 1999). Among women in Western countries, evidence suggests that the risks of upper digestive cancer (e.g., stomach cancer) and lung cancer show an inverse socioeconomic gradient (i.e., a reduced cancer risk with higher SES) (Faggiano, Partanen, Kogevinas, & Boffetta, 1997). The fundamental cause theory of SES and health—developed by Link and Phelan in 1995—argues that the robust association between SES and health arises because SES "embodies an array of resources, such as money, knowledge, prestige, power, and beneficial social connections that protect health no matter what mechanisms are relevant at any given time." (Link & Phelan, 1995) For example, the connection between SES and stomach cancer and lung cancer can be explained by socioeconomic disparities in smoking, alcohol drinking, and other health behaviors (Faggiano et al., 1997; Krieger et al., 1999; Uthman, Jadidi, & Moradi, 2013; Weiderpass & Pukkala, 2006).

However, higher SES does not protect against the risk of cancer in every instance. For example, breast cancer tends to show a positive socioeconomic gradient (i.e., an excess cancer risk with higher SES). That finding has been attributed to socioeconomic differences in reproductive behavior, e.g., overall fertility, age at first birth, and spacing of births (Faggiano et al., 1997; Larsen et al., 2011). Thus, it would be more accurate to state that higher SES tends to be associated with better (overall) health irrespective of the relevant mechanisms at any given time; however, *specific* health outcomes (e.g., breast cancer) can be positively correlated with high SES depending on the background context.

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To our knowledge, although some studies on the socioeconomic gradient in cancer *mortality* (though not cancer incidence) are available (Eguchi, Wada, Prieto-Merino, & Smith, 2017; Tanaka et al., 2017), the documentation of socioeconomic inequalities in female cancer incidence remains sparse in Asian countries, including Japan. Sex differences exist in the etiology of cancer (e.g., frequency, pathology, and survival) (Hori et al., 2015; Zaitsu et al., 2015), and the distribution of higher SES (professionals and managers) in women is different from that in men in Japan (Tanaka et al., 2017). In addition, the risk associated with homemakers has not yet been identified. Therefore, it is necessary to determine the socioeconomic disparities in female cancer incidence in Japan separately from those with males.

Using a nationwide inpatient dataset that included details of occupational class (with homemakers as a separate category) as a proxy for SES (Mannetje & Kromhout, 2003), we examined whether a socioeconomic gradient was associated with the risks for overall and site-specific cancer incidence among women in Japan. We also determined whether any observed socioeconomic gradient remained even after controlling for mediation by major modifiable behavioral factors (smoking and alcohol consumption).

2. Methods

2.1. Study setting

We conducted a hospital-based matched case-control study using female patient data (1984–2016) from the nationwide clinical and occupational database of the Rosai Hospital group, run by the Japan Organization of Occupational Health and Safety (JOHAS), an independent administrative agency. Details of the database have been described elsewhere (Kaneko, Kubo, & Sato, 2015; Zaitsu, Kawachi, Takeuchi, & Kobayashi, 2017; Zaitsu et al., 2016). Briefly, the Rosai Hospital group consists of 34 general hospitals in major urban areas of Japan; it has collected medical chart information (including basic sociodemographic characteristics, clinical history and diagnosis, pathological information, treatment, and outcomes for every inpatient) since 1984. The clinical diagnosis, extracted from physicians' medical charts confirmed at discharge, is coded according to the International Classification of Diseases and Related Health Problems, 9th Revision (ICD-9) or 10th Revision (ICD-10) (Kaneko et al., 2015; Zaitsu et al., 2016, 2017). From questionnaires completed at the time of admission, the database includes the occupational history of each inpatient (current and three most recent jobs, including the age of starting and ending) as well as smoking and alcohol habits. The detailed occupational history is coded using the standardized three-digit codes of the Japan Standard Occupational Classification and Japan Standard Industrial Classification; they correspond, respectively, to the International Standard Industrial Classification and International Standard Occupational Classification (Kaneko et al., 2015; Zaitsu et al., 2016, 2017). According to the revisions of the Japan Standard Occupational Classification and Japan Standard Industrial Classification during the study period, JOHAS updated the previous job codes to be consistent with changes in coding practice (Zaitsu et al., 2016). Written informed consent was obtained before patients completed the questionnaires; trained registrars and nurses are responsible for registering the data. The database currently contains details from over 6 million inpatients.

2.2. Cases and controls

The study subjects comprised 846,963 female patients (143,806 cancer cases, 703,157 hospital controls) aged 20 years or older admitted to hospital between 1984 and 2016. Controls for each cancer case were matched by sex, age (same 5-year age category), admission date (same financial year), and hospital (Zaitsu et al., 2016). We randomly sampled five controls for each cancer case; however, the matching process generated fewer than five controls for some cancer cases. The matched background characteristics (age, admission date, and admitting hospital) were well balanced between the cases and controls: e.g., mean age of the cases and controls was, respectively, 65 years (SD 14.5 years) and 64 years (SD 14.4 years).

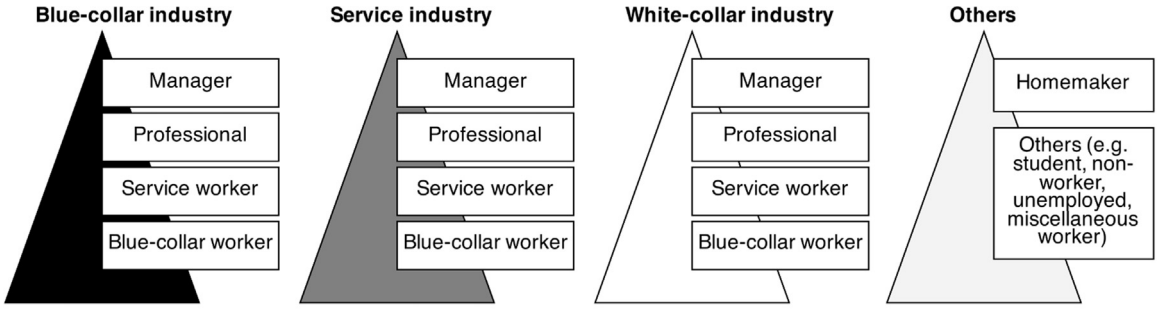
The cancer cases were those patients whose main diagnoses were cancer, confirmed by physicians on discharge, for the first-time stay in the hospitals for the initial cancer, together with pathological or imaging information (e.g., computed tomography, magnetic resonance imaging, and endoscopy); they did not have a previous history of malignant disease (Zaitsu et al., 2016, 2017). We defined cancer incidence by the diagnosis of cancer cases; the validation for the diagnosis corresponding to ICD-9 or ICD-10 in the database has been described elsewhere (Kaneko et al., 2015; Zaitsu et al., 2016, 2017). The database is unique to the Rosai Hospital group and so differs from medical claims data, which may have less diagnostic accuracy (Sato, Yagata, & Ohashi, 2015). Following national statistics for Japan (Hori et al., 2015), we specified the top 10 common female cancer sites: breast (17.4%); colon and rectum (13.8%); stomach (13.8%); lung (5.7%); liver (4.7%); pancreas (2.9%); gallbladder (2.2%); malignant lymphoma (3.3%); cervix (4.8%); and uterus (3.1%; Supplementary Table 1). Less common cancers (from 14 sites) were additionally specified. The prevalence of these cancers was almost identical to that in national statistics (Supplementary Table 1) (Hori et al., 2015). The total of female cancer cases in the present study amounted to 1.9% of the total expected female cancer cases in Japan for the years 1984–2013 (134,767 of 6,925,517) (Hori et al., 2015).

Our control subjects comprised female patients who were admitted to hospital with a diagnosis of the following: eye or ear diseases (ICD-9, 360–389 and ICD-10, H00–H95; 37.0%); genitourinary system diseases (ICD-9, 580–629 and ICD-10, N00–N99; 24.4%); infectious or parasitic diseases (ICD-9, 1–136 and ICD-10, A00–B99; 10.7%); skin diseases (ICD-9, 680–709 and ICD-10, L00–L99; 5.1%); symptoms and abnormal findings, such as dizziness and chest and abdominal pain (ICD-9, 780–799 and ICD-10, R00–R99; 9.4%); or other diseases, such as congenital malformation (ICD-9, 280–289, 740–779, and ICD-10, D50–D77, P00–P96, Q00–Q99; 13.4%) (Zaitsu et al., 2016, 2017). Estimating odds for each control disease against the rest of the other five control diseases in a prior analysis within 124,087 control subjects, we assumed that these diagnoses selected for the control group were not linked to SES (Supplementary Fig. 1).

2.3. SES grouped by occupation and industry combination and other covariates

We selected the longest-held job for each patient from her occupational history to categorize SES. Owing to the enormous variety of occupations in the dataset, we aggregated the longest-held occupational class into four major occupational groupings (Galobardes, Shaw, Lawlor, Lynch, & Davey Smith, 2006; Mannetje & Kromhout, 2003; Tanaka et al., 2017): blue-collar workers, service workers, professionals, and managers. We additionally cross-classified the longest-held occupations into three industrial sectors (Jackson, Redline, Kawachi, Williams, & Hu, 2013; Mannetje & Kromhout, 2003; Tanaka et al., 2017): blue-collar industry, service industry, and white-collar industry (Fig. 1). Further, within the "others" group (comprising homemakers, students, non-workers, unemployed, and miscellaneous workers) (Zaitsu et al., 2018), we distinguished between homemakers and the remainder (Fig. 1). The major profile of SES among the study subjects did not largely differ from that in national statistics (Supplementary Table 2). The average length of the longest held jobs was 27 years.

Age, admission date, and admitting hospital were confounding factors (Zaitsu et al., 2016, 2017). The major modifiable behavioral factors, i.e., smoking (pack-years) and alcohol consumption (daily amount), were mediating factors (Zaitsu et al., 2016, 2017).



Occupational class	Japan Standard Occupational Classification	2-digit code
Blue-collar worker	Security, agriculture, forestry, fishery, manufacturing, transport and machine operation (stationary and construction machinery operators, construction, mining, carrying, cleaning, packaging, and related workers)	43–59, 64–73
Service worker	Clerical, sales, service, and transport and machine operation (railway drivers, motor vehicle drivers, ship and aircraft operators, and other transport related workers)	25–42, 60–63
Professional	Professional and engineering workers	05–24
Manager	Administrative and managerial workers	01–04
Industrial cluster	**Japan Standard Industrial Classification**	**Major code**
Blue-collar industry*	Agriculture, forestry, fisheries, mining, quarrying of stone, construction, manufacturing, electricity, gas, heat supply, water, transport, and postal service	A–F, H
Service industry	Wholesale, retail trade, accommodations, eating, drinking, living-related, personal, amusement, and compound services, services not elsewhere categorized	I, M, N, Q, R
White-collar industry†	Information, communications, finance, insurance, real estate, goods rental, leasing, education, learning support, medical, healthcare, welfare, and government except elsewhere classified	G, J, K, L, O, P, S

* Waste disposal business (Code R88) included. † Political, business and cultural organizations (Code R93), railway transport (Code H42), road passenger transport (Code H43), and air transport (Code H46) included.

Fig. 1. Socioeconomic status grouped by longest-held occupational class cross-classified with industrial cluster.

2.4. Statistical analysis

We performed multiple imputation for missing data among the 846,963 study subjects using all data, including SES, smoking, and alcohol consumption; five imputed datasets were generated (Zaitsu, Kawachi, Ashida, Kondo, & Kondo, 2018). The following missing data were multiply imputed: SES (285,737, 33.7%), smoking (267,392, 31.6%), and alcohol consumption (346,150, 40.9%). The basic demographics (i.e., age, admission date, and admitting hospital) were similar between those with complete and incomplete data for SES; however, some lifestyle habits such as smoking and drinking differed between those with complete and incomplete data. Excluding incomplete data may lead to biased inference; therefore, we conducted multiple imputation analysis (Supplementary Table 3).

Using blue-collar workers in blue-collar industries as the referent category, we estimated odds ratios (ORs) and 95% confidence intervals (CIs) in each SES for each specific cancer site as well as overall cancer incidence. For primary analysis to assess baseline socioeconomic gradients in female cancer incidence, we used conditional logistic regression with multiple imputation matched for age, admission date, and admitting hospital (model 1) (Zaitsu et al., 2016, 2018). The five ORs and 95% CIs obtained at each imputed dataset were combined into one combined OR and 95% CI. To assess the contribution of major modifiable behavioral factors, we additionally adjusted for smoking and alcohol consumption as mediation factors (model 2).

For sensitivity analysis, we restricted the analysis to never smokers (82,969 cases, 341,792 controls). Owing to the insufficient number of the cases for less common types, we limited the analysis to overall and the top 10 common cancers. Additionally, we performed conditional logistic regression for patients with complete information (84,848 cases, 396,677 controls) without performing multiple imputation. For Supplementary data analysis using an alternative control group (all available controls with all benign diseases matched for age, diagnostic data, and admitting hospital), we performed conditional logistic regression with multiple imputation for stomach cancer (19,840 cases, 99,160 controls) and breast cancer (24,983 cases, 124,905 controls). Alpha was set at 0.05, and all *P* values were two-sided. Data were analyzed using STATA/MP13.1 (Stata-Corp LP, College Station, TX).

3. Results

Among the top 10 common female cancers in Japan, we observed an inverse socioeconomic gradient (i.e., reduced risk with higher SES) for stomach and lung cancers (Fig. 2). In blue- and white-collar industries, higher SES (professionals and managers) had lower odds for stomach cancer (the OR ranged from 0.68 for managers in blue-collar industries to 0.77 for professionals in white-collar industries) and lung cancer (OR 0.47 for managers in blue-collar industries; Table 1). Even after fully controlling for smoking and alcohol consumption, the observed lower odds in higher SES were not attenuated; they remained significantly associated with stomach cancer (adjusted OR ranged from 0.67 for managers in blue-collar industries to 0.78 for professionals in white-collar industries) and lung cancer (adjusted OR 0.40 for managers in blue-collar industries, model 2, Table 1). Homemakers showed a similar trend to subjects with higher SES (Fig. 2); however, the magnitude of the OR was weaker than those with higher SES (adjusted OR, 0.80 for

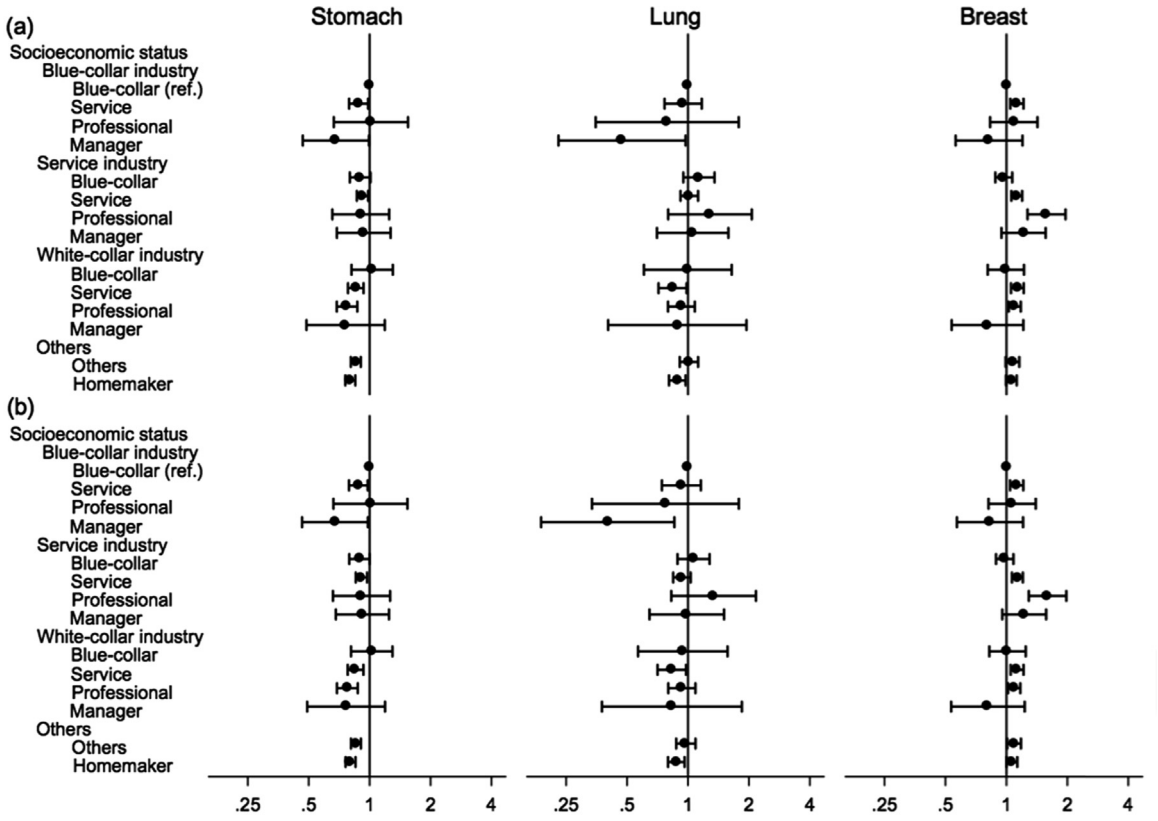


Fig. 2. Socioeconomic gradients associated with risk for incidence of stomach, lung, and breast cancers. The odds ratio (dot) and 95% confidence interval (bar) were estimated by conditional logistic regression, (a) matched for age, admission date, and admitting hospital and (b) additionally adjusted for smoking and alcohol consumption, with five imputed datasets. The numbers of cases and controls used for analysis were, respectively, 19,840 and 96,658 for stomach cancer, 8,207 and 39,941 for lung cancer, and 24,983 and 122,414 for breast cancer.

stomach cancer and 0.87 for lung cancer, model 2, Table 1).

By contrast, we found a positive socioeconomic gradient (i.e., excess risk with higher SES) for breast cancer (Fig. 2). In service and white-collar industries, higher SES showed higher odds for breast cancer (OR ranged from 1.10 for professionals in white-collar industries to 1.58 for professionals in service industries; Table 2). Even after fully controlling for smoking and alcohol consumption, the observed higher odds with higher SES were not attenuated and remained significantly associated with breast cancer (adjusted OR ranged from 1.09 for professionals in white-collar industries to 1.60 for professionals in service industries, model 2, Table 2). The risk for homemakers (as well as service workers in all industries) was again similar to subjects with higher SES (Fig. 2); however, the magnitude of the OR was weaker than those with higher SES (adjusted ORs ranged from 1.06 for homemakers to 1.13 for service workers in service and white-collar industries, model 2, Table 2).

Among the remainder of common cancers, we observed no socioeconomic gradient (i.e., reduced or excess risk with higher SES); however, pancreatic, gallbladder, malignant lymphoma, and cervical cancer appeared to hint at a possible inverse gradient pattern (Supplementary Fig. 2, Supplementary Table 4). The overall cancer incidence showed a weak inverse socioeconomic gradient (Fig. 3), which persisted even after fully controlling for smoking and alcohol consumption (adjusted OR ranged from 0.84 for managers in white-collar industries to 0.91 for professionals in white-collar industries, model 2, Table 2).

Less common cancers did not show a socioeconomic gradient (Supplementary Fig. 3); however, certain cancers (e.g., those of the oral cavity, pharynx, and esophagus) appeared to show a possible inverse gradient pattern (Supplementary Table 4). In the sensitivity analysis, although the precise odds estimated with various regression analyses differed according to the analytic model and analyzed population, the direction of the socioeconomic gradient was almost identical (Supplementary Figs. 4 and 5). Likewise, the results from the alternative control group (i.e., all benign diseases) showed the same socioeconomic gradient pattern (Supplementary Fig. 6). In addition, smoking and alcohol consumption were independently associated with most of the risk for site-specific and overall cancer incidence, regardless of SES (Supplementary Table 5 and 6).

4. Discussion

4.1. All cancer sites

Studies in Western countries suggest a slightly inverse socioeconomic gradient in such nations as Finland; in some instances, there is a fairly flat gradient for overall female cancer incidence in Denmark, Sweden, and France (Faggiano et al., 1997; Melchior et al., 2005). With the Japanese data in the present study, we found a weak inverse overall socioeconomic gradient; this result suggests that the inverse socioeconomic gradients for stomach and lung cancers (which made up approximately 20% of all incident cancers) were partially canceled by the positive socioeconomic gradient for breast cancer (accounting for 18% of all incident cancer).

4.2. Stomach cancer

An inverse socioeconomic gradient for stomach cancer has been consistently reported in Western countries (Faggiano et al., 1997; Spadea et al., 2010; Weiderpass & Pukkala, 2006). A recent systematic review reached the same conclusion (Uthman et al., 2013). This pattern may be partly due to less smoking and drinking with higher SES (Uthman et al., 2013; Weiderpass & Pukkala, 2006). However, in the present study, an inverse socioeconomic gradient persisted after

Table 1
Odds ratios for each socioeconomic status associated with risk for female stomach and lung cancer incidence.

		Control, %	Case, %	Model 1[a]		Model 2[b]	
				OR (95% CI)	*P*	OR (95% CI)	*P*
Stomach							
n		96,658	19,840				
SES							
Blue-collar industry	Blue-collar worker	16.9	19.3	1.00		1.00	
	Service worker	3.7	3.7	0.88 (0.79–0.98)	.02	0.88 (0.79–0.98)	.02
	Professional	0.2	0.2	1.01 (0.67–1.55)	.94	1.01 (0.66–1.54)	.97
	Manager	0.4	0.3	0.68 (0.47–0.99)	.05	0.67 (0.46–0.98)	.04
Service industry	Blue-collar worker	2.5	2.6	0.90 (0.80–1.01)	.07	0.89 (0.79–1.00)	.05
	Service worker	12.8	13.5	0.92 (0.86–0.98)	.01	0.91 (0.85–0.97)	.005
	Professional	0.2	0.2	0.90 (0.65–1.25)	.54	0.91 (0.66–1.26)	.58
	Manager	0.4	0.5	0.94 (0.69–1.27)	.66	0.92 (0.68–1.25)	.58
White-collar industry	Blue-collar worker	0.4	0.5	1.03 (0.81–1.30)	.81	1.02 (0.81–1.30)	.84
	Service worker	4.7	4.6	0.85 (0.78–0.93)	< .001	0.85 (0.78–0.93)	< .001
	Professional	4.8	4.3	0.77 (0.69–0.87)	< .001	0.78 (0.69–0.87)	< .001
	Manager	0.2	0.2	0.76 (0.49–1.19)	.22	0.76 (0.49–1.19)	.23
Others	Others	20.2	20.0	0.85 (0.81–0.90)	< .001	0.86 (0.81–0.91)	< .001
	Homemaker	32.6	30.3	0.80 (0.76–0.85)	< .001	0.80 (0.76–0.85)	< .001
Smoking							
	Never	73.7	73.6			1.00	
	≤20 pack-year	22.5	21.2			0.95 (0.89–1.00)	.07
	> 20–40 pack-year	2.9	3.9			1.31 (1.20–1.43)	< .001
	> 40 pack-year	0.8	1.4			1.59 (1.38–1.84)	< .001
Alcohol consumption							
	Never	70.5	71.2			1.00	
	≤15 g/day	17.7	15.9			0.89 (0.85–0.95)	< .001
	> 15–30 g/day	10.1	10.6			1.02 (0.96–1.09)	.50
	> 30 g/day	1.8	2.3			1.17 (1.02–1.34)	.02
Lung							
n		39,941	8,207				
SES							
Blue-collar industry	Blue-collar worker	15.4	16.2	1.00		1.00	
	Service worker	3.7	3.6	0.95 (0.77–1.17)	.59	0.93 (0.74–1.16)	.48
	Professional	0.1	0.1	0.79 (0.35–1.78)	.56	0.77 (0.34–1.78)	.54
	Manager	0.4	0.2	0.47 (0.23–0.97)	.04	0.40 (0.19–0.86)	.02
Service industry	Blue-collar worker	2.5	3.0	1.13 (0.95–1.35)	.17	1.07 (0.89–1.28)	.49
	Service worker	12.6	13.4	1.01 (0.92–1.12)	.77	0.93 (0.84–1.03)	.17
	Professional	0.2	0.3	1.28 (0.80–2.07)	.30	1.34 (0.83–2.17)	.24
	Manager	0.4	0.5	1.05 (0.70–1.58)	.80	0.99 (0.65–1.51)	.95
White-collar industry	Blue-collar worker	0.4	0.4	1.00 (0.61–1.65)	.99	0.94 (0.57–1.57)	.81
	Service worker	4.5	4.0	0.84 (0.72–0.98)	.03	0.83 (0.71–0.98)	.03
	Professional	4.5	4.3	0.93 (0.80–1.08)	.33	0.93 (0.80–1.09)	.37
	Manager	0.2	0.2	0.89 (0.40–1.95)	.75	0.83 (0.38–1.84)	.63
Others	Others	18.8	20.1	1.01 (0.91–1.12)	.85	0.98 (0.87–1.09)	.65
	Homemaker	36.2	33.7	0.89 (0.81–0.97)	.01	0.87 (0.80–0.96)	.006
Smoking							
	Never	72.8	64.0			1.00	
	≤20 pack-year	22.9	23.2			1.23 (1.13–1.33)	< .001
	> 20–40 pack-year	3.2	7.9			2.98 (2.68–3.32)	< .001
	> 40 pack-year	1.0	4.9			5.76 (4.94–6.71)	< .001
Alcohol consumption							
	Never	68.7	68.4			1.00	
	≤15 g/day	18.4	16.2			0.81 (0.71–0.92)	.004
	> 15–30 g/day	11.0	12.2			0.92 (0.80–1.05)	.19
	> 30 g/day	1.9	3.2			0.96 (0.79–1.17)	.70

[‡]Data were estimated with five imputed datasets. Percentages may not total 100 because of rounding with multiple imputation. OR, odds ratio; CI, confidence interval; SES, socioeconomic status.

[a] Conditional logistic regression matched for age, admission date, and admitting hospital.

[b] Additional adjustment for smoking and alcohol consumption.

controlling for potential mediation by smoking and drinking. Other factors may therefore play a role.

In Japan, dietary habits (e.g., higher consumption of salty food with lower SES associated with the risk of stomach cancer) could be a potential explanation (Miyaki et al., 2013; Umesawa et al., 2016). *Helicobacter pylori* infection is an additional explanation: the probability of infection in childhood is likely to be lower among individuals with high SES than in those with low SES (Uthman et al., 2013). However, *H. pylori* infection was not a predictor of the incidence of stomach cancer among women in the Hisayama cohort in Japan (but it was a predictor for men); that is partially because of the high prevalence of *H. pylori* infection (approximately 63%) and potential uncontrolled confounders, such as SES (Yamagata et al., 2000).

To some extent in Japan, national cancer screening is associated with the prevention of stomach cancer (Leung et al., 2008). With regard to treatment access, the universal health coverage system may be attributable to the reduction in the SES gap for stomach cancer *mortality*. However, for prevention, the SES gap for cancer screening may exist because municipalities provide cancer screening for homemakers and workers in small companies; health insurance groups at workplaces

Table 2
Odds ratios for each socioeconomic status associated with risk for female breast and overall cancer incidence.

		Control, %	Case, %	Model 1[a]		Model 2[b]	
				OR (95% CI)	*P*	OR (95% CI)	*P*
Breast							
n		122,414	24,983				
SES							
Blue-collar industry	Blue-collar worker	12.9	12.1	1.00		1.00	
	Service worker	5.6	5.9	1.13 (1.05–1.21)	.002	1.12 (1.04–1.21)	.002
	Professional	0.3	0.3	1.09 (0.83–1.42)	.55	1.07 (0.82–1.40)	.63
	Manager	0.3	0.2	0.82 (0.56–1.20)	.30	0.83 (0.57–1.21)	.31
Service industry	Blue-collar worker	3.1	2.8	0.97 (0.88–1.07)	.53	0.98 (0.89–1.08)	.69
	Service worker	17.6	18.4	1.12 (1.06–1.20)	< .001	1.13 (1.06–1.21)	< .001
	Professional	0.4	0.5	1.58 (1.27–1.96)	< .001	1.60 (1.29–1.98)	< .001
	Manager	0.3	0.4	1.21 (0.94–1.56)	.13	1.22 (0.95–1.57)	.11
White-collar industry	Blue-collar worker	0.5	0.5	0.99 (0.81 − 1.22)	.95	1.01 (0.82–1.24)	.91
	Service worker	7.5	7.8	1.13 (1.05–1.22)	.001	1.13 (1.05 − 1.21)	.001
	Professional	7.6	7.7	1.10 (1.03–1.18)	.007	1.09 (1.02–1.17)	.01
	Manager	0.2	0.2	0.81 (0.54–1.21)	.29	0.81 (0.53–1.23)	.31
Others	Others	11.0	11.0	1.07 (0.99–1.16)	.08	1.09 (1.01–1.18)	.03
	Homemaker	32.8	32.2	1.06 (0.99–1.12)	.08	1.06 (1.00–1.13)	.05
Smoking							
	Never	68.9	73.0			1.00	
	≤20 pack-year	25.9	21.6			0.76 (0.73–0.80)	< .001
	> 20–40 pack-year	4.3	4.4			0.92 (0.85–0.98)	.02
	> 40 pack-year	0.9	1.0			0.99 (0.85–1.14)	.86
Alcohol consumption							
	Never	60.0	61.3			1.00	
	≤15 g/day	20.8	17.6			0.87 (0.83–0.91)	< .001
	> 15–30 g/day	15.9	17.3			1.12 (1.06–1.19)	< .001
	> 30 g/day	3.4	3.8			1.16 (1.06–1.26)	< .001
Overall							
n		703,157	143,806				
SES							
Blue-collar industry	Blue-collar worker	14.7	15.1	1.00		1.00	
	Service worker	4.4	4.5	1.00 (0.97–1.04)	.92	1.00 (0.96–1.04)	.97
	Professional	0.2	0.2	0.86 (0.73–1.00)	.06	0.85 (0.73–0.99)	.04
	Manager	0.3	0.3	0.87 (0.76–0.99)	.03	0.85 (0.75–0.97)	.02
Service industry	Blue-collar worker	2.7	2.6	0.96 (0.92–1.00)	.07	0.95 (0.91–1.00)	.04
	Service worker	14.4	15.2	1.04 (1.01–1.06)	.002	1.02 (1.00–1.05)	.04
	Professional	0.3	0.3	1.09 (0.98–1.21)	.11	1.09 (0.98–1.22)	.09
	Manager	0.4	0.4	0.97 (0.85–1.11)	.66	0.95 (0.83–1.09)	.48
White-collar industry	Blue-collar worker	0.4	0.5	1.01 (0.90–1.13)	.89	1.01 (0.89–1.13)	.92
	Service worker	5.7	5.5	0.95 (0.92–0.98)	.004	0.95 (0.92–0.98)	.003
	Professional	5.8	5.4	0.91 (0.88–0.94)	< .001	0.91 (0.88–0.94)	< .001
	Manager	0.2	0.2	0.84 (0.73–0.98)	.02	0.84 (0.72–0.97)	.02
Others	Others	16.5	17.1	1.00 (0.98–1.03)	.87	1.00 (0.98–1.03)	.70
	Homemaker	33.9	32.7	0.94 (0.92–0.96)	< .001	0.95 (0.93–0.96)	< .001
Smoking							
	Never	71.6	71.5			1.00	
	≤20 pack-year	24.1	22.6			0.94 (0.93–0.96)	< .001
	> 20–40 pack-year	3.4	4.5			1.28 (1.24–1.32)	< .001
	> 40 pack-year	0.9	1.4			1.58 (1.50–1.66)	< .001
Alcohol consumption							
	Never	66.0	66.9			1.00	
	≤15 g/day	19.1	16.9			0.88 (0.86–0.90)	< .001
	> 15–30 g/day	12.6	13.2			1.03 (1.00–1.06)	.08
	> 30 g/day	2.3	3.0			1.16 (1.10–1.22)	< .001

‡Data were estimated with five imputed datasets. Percentages may not total 100 because of rounding with multiple imputation. OR, odds ratio; CI, confidence interval; SES, socioeconomic status.

[a] Conditional logistic regression matched for age, admission date, and admitting hospital.

[b] Additional adjustment for smoking and alcohol consumption.

provide screening for workers in large industries (Ikeda et al., 2011; Tanaka et al., 2017). The proportion of individuals undergoing cancer screening is greater in the latter category; people with higher SES tend to undergo regular cancer screening (Chor et al., 2014; Ikeda et al., 2011; Kweon, Kim, Kang, Shin, & Choi, 2017). Indeed, in the present study, the odds for homemakers (adjusted OR 0.80) were weaker than subjects with higher SES (adjusted OR 0.67 for managers in blue-collar industries).

4.3. Lung cancer

Lung cancer is strongly socially patterned; one Swedish study found the population-attributable fraction of socioeconomic differences to be over 50% (Hemminki, Zhang, & Czene, 2003). In Japan, we still identified a steep residual inverse socioeconomic gradient even after controlling for smoking; that corresponds to a population-attributable fraction of 59% for the maximum SES gap.

Veglia et al., (2007) reported work-related secondhand tobacco smoke exposure (hazard ratio, 1.6). In particular, the blue-collar sector

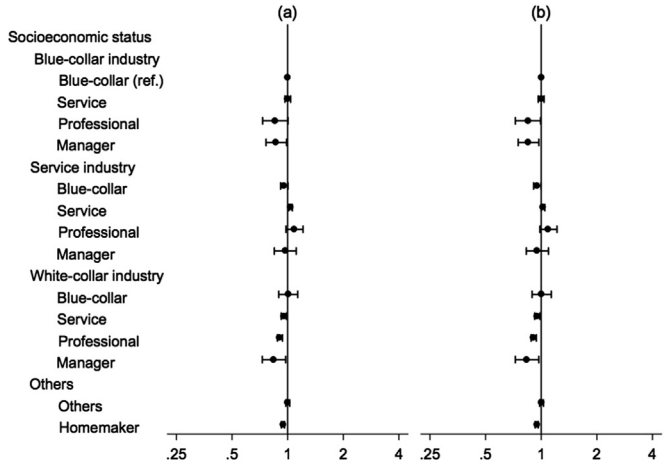


Fig. 3. Socioeconomic gradient associated with risk for overall female cancer incidence. The odds ratio (dot) and 95% confidence interval (bar) were estimated by conditional logistic regression, (a) matched for age, admission date, and admitting hospital and (b) additionally adjusted for smoking and alcohol consumption, with five imputed datasets. The numbers of cases and controls used for analysis were, respectively, 143,806 and 703,157.

workplace (e.g., manufacturing), which was the most popular workplace for women in Japan in the study period (Tanaka et al., 2017), may be more lax with regard to limiting secondhand tobacco smoke exposure (Howard, 2004). Indeed, national legislation to restrict indoor smoking has yet to be established in Japan.

4.4. Breast cancer

A positive socioeconomic gradient in breast cancer, which has been documented in many countries (Faggiano et al., 1997), may partially represent causal pathways linked to reproductive and fertility behaviors. In particular, evidence suggests that a greater risk of breast cancer incidence with higher SES is associated with relevant breast cancer risks, i.e., older age at birth of first child, use of hormone replacement therapy, and higher consumption of alcohol (Larsen et al., 2011). Indeed, alcohol consumption was associated with breast cancer risk in our study: a 12%–16% increase was evident among moderate to heavy drinkers ($>$ 15 g ethanol per day).

We identified a positive socioeconomic gradient even after controlling for possible confounding and mediating factors. There could be potential mediation related to stress; women with higher SES are associated with interpersonal stress in the workplace (Pudrovska, Carr, McFarland, & Collins, 2013). The odds for homemakers were weaker than service workers or subjects with higher SES. This finding suggests that homemakers may have limited access to resources to promote their health (e.g., breast cancer screening) (Zaitsu et al., 2018); alternatively, homemakers may have working stress to a lesser extent at home, their main workplace. Additionally, the likelihood of undergoing breast cancer screening may be higher in individuals with higher SES, which is associated with overdiagnosis (Chor et al., 2014; Kweon et al., 2017; Jacklyn, Glasziou, Macaskill, & Barratt, 2016). With potential mediation through sleep disturbance and telomere shortening, breast cancer risk may be associated with night shift workers, such as nurses (Samulin Erdem et al., 2017; Yuan et al., 2018). In fact, we observed elevated odds among professionals in white-collar industries, which was comprised with ~40% of medical professionals, including nurses and physicians.

4.5. Remaining common cancers and less common cancers

We did not observe a socioeconomic gradient for the remaining common cancers and less common cancers. However, a possible inverse socioeconomic gradient was evident for several upper digestive and gynecologic sites, which concurs with Western trends (Faggiano et al., 1997; Spadea et al., 2010). A null socioeconomic gradient for colorectal cancer and a tendency for an inverse socioeconomic gradient for pancreatic and gallbladder cancers (which has not been consistently reported in Western countries) may be associated with healthier dietary patterns in Japan (e.g., eating more vegetables and fish) (Faggiano et al., 1997; Qiu et al., 2005; Song et al., 2016). For malignant lymphoma, a positive socioeconomic gradient has been found with some types of malignant lymphoma in the United States (Clarke, Glaser, Gomez, & Stroup, 2011). That gradient has shown mostly no association with SES worldwide (Faggiano et al., 1997), and we observed a possible inverse pattern. For other less common cancers, the literature is sparse (Faggiano et al., 1997).

4.6. Strengths and limitations

Using a large, nationwide clinical and occupational dataset, we have for the first time provided a comprehensive picture of socioeconomic inequalities in female cancer incidence in Japan. This study is one of the largest studies conducted for female cancer incidence in that country. In addition, the strengths of this study include accurate cancer diagnoses directly extracted from medical charts in contrast to less accurate ones used in previous studies with claims data (Sato et al., 2015). A further strength of the study is the relatively low job turnover in Japan, which meant less possibility of misclassification. It is estimated that on average 30% of women do not change jobs during working ages, while an additional 20% changed jobs just once (Ministry of Health, Labour and Welfare, 2014). The average length of the longest held jobs was 27 years. In contrast to previous studies, which assigned the most recent occupation as a proxy for SES recorded on the death certificate (Eguchi et al., 2017; Tanaka et al., 2017), the longest-held occupation is less likely to reflect misclassification owing to reverse causality: patients may change their jobs or become inactive in the labor force following cancer diagnosis. Although the national standard classification was revised over time, JOHAS updated the job codes to be consistent with standard practice, and we do not feel that significant misclassification was introduced (Zaitsu et al., 2016).

Some limitations, however, should be noted. First, the selection of hospital controls was subject to selection bias. The absence of relevant population-based data did not allow us to obtain population-based controls (e.g., as in a population-based case-control study in the Nordic Occupational Cancer Study) (Talibov et al., 2018); however, the analysis with the alternative control group (patients with all benign diseases) showed the same patterns and directions of the socioeconomic gradient. In addition, one-third of the missing information may have introduced selection bias—even though multiple imputation was performed; however, the sensitivity analysis with completed data showed the same socioeconomic gradient. The self-reported information on admission is another possible limitation inherent in recall bias.

Second, our measured occupational class is not a perfect proxy for SES, and other relevant socioeconomic factors, i.e., educational attainment and income levels, and the timing of the longest-held job were not assessed owing to the limitations of our dataset (Larsen et al., 2011; Spadea et al., 2010). However, a study with data from all residents in Finland showed occupational class differences in cancer incidence—even within strata of educational attainment and income levels (Weiderpass & Pukkala, 2006). In addition, our broad category of the longest-held occupational class was not designed to capture occupational exposure; therefore, it is different from detailed occupational classes defined in studies for detecting specific occupational cancer incidence (Barry et al., 2017; Talibov et al., 2018; Weiderpass & Pukkala, 2006). We could not assess the partners' SES of married women, which may be independently associated with women's SES (over and above her own occupation) (Honjo et al., 2012). Additionally, although the prevalence of each specific cancer is consistent with

national statistics (Hori et al., 2015), our analyzed cases represented only 1.9% of the total cases of female cancer incidence in the whole country. Hence, the generalizability of our findings to the rest of Japan may be limited.

Finally, we assessed the contribution of major modifiable behavioral factors of smoking and alcohol consumption on the socioeconomic gradient; however, the data limitations did not enable us to assess other possible mediation factors such as diet, physical activity, and night shift work (Qiu et al., 2005; Samulin Erdem et al., 2017; Talibov et al., 2018; Takao, Kawakami, & Ohtsu, 2003; Yuan et al., 2018), or evaluate socioeconomic inequalities, including employment status (full-time, precarious, and unemployed workers) that might have potential impacts on cancer risk through psychological distress or access to healthcare service (Singer et al., 2016; Tsurugano, Inoue, & Yano, 2012), within the strata of cancer stage at diagnosis by linkage of SES information to local cancer registries (Kweon et al., 2017; Zaitsu et al., 2015). Therefore, future studies, such as ones concentrating on molecular pathological epidemiology (Ogino et al., 2016), are warranted to integrate all aspects of cancer causal pathways.

5. Conclusion

We observed socioeconomic inequalities in female cancer incidence in Japan—even after controlling for smoking and alcohol consumption. The national cancer prevention strategy in Japan needs to explicitly incorporate strategies to address socioeconomic inequalities.

Ethics approval and consent to participate

Written informed consent was obtained, and the research ethics committees of The University of Tokyo, Tokyo (Protocol Number 3890-3) and Kanto Rosai Hospital, Kanagawa (Protocol Number 2014-38) approved the study.

Availability of data and material

The data that support the findings of this study are available from JOHAS, but restrictions apply to the availability of these data; they were used under the research agreement for the current study and so are not publicly available. If any person wishes to verify our data, they are most welcome to contact the corresponding author.

Conflict of interest

The authors declare no conflict of interest.

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Authors' contributions

MZ and IK originated the idea and designed the study. MZ conducted the analysis and wrote the manuscript draft. All authors interpreted the analyses and critically reviewed and edited the manuscript. All authors read and approved the final manuscript.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.ssmph.2018.06.001.

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ORIGINAL RESEARCH

WILEY Cancer Medicine Open Access

Occupational class and male cancer incidence: Nationwide, multicenter, hospital-based case–control study in Japan

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Abstract

Little is known about socioeconomic inequalities in male cancer incidence in nonwestern settings. Using the nationwide clinical and occupational inpatient data (1984-2016) in Japan, we performed a multicentered, matched case–control study with 214 123 male cancer cases and 1 026 247 inpatient controls. Based on the standardized national classifications, we grouped patients' longest-held occupational class (blue-collar, service, professional, manager), cross-classified by industrial cluster (blue-collar, service, white-collar). Using blue-collar workers in blue-collar industries as the referent group, odds ratios (ORs) and 95% confidence intervals (CIs) were estimated by conditional logistic regression with multiple imputation, matched for age, admission date, and admitting hospital. Smoking and alcohol consumption were additionally adjusted. Across all industries, a reduced risk with higher occupational class (professionals and managers) was observed for stomach and lung cancer. Even after controlling for smoking and alcohol consumption, the reduced odds persisted: OR of managers in white-collar industries was 0.80 (95% CI 0.72-0.90) for stomach cancer, and OR of managers in white-collar industries was 0.66 (95% CI 0.55-0.79) for lung cancer. In white-collar industries, higher occupational class men tended to have lower a reduced risk for most common types of cancer, with the exception of professionals who showed an excess risk for prostate cancer. We documented socioeconomic inequalities in male cancer incidence in Japan, which could not be explained by smoking and alcohol consumption.

KEYWORDS

cancer incidence, Japan, occupation, risk, socioeconomic status

1 | INTRODUCTION

Cancer is a leading cause of death in developed countries, and in 2016, the total incidence of cancer was estimated to be 867 408 (male 501 527 and female 365 881) in Japan.[1] Although overall cancer mortality has been declining in Japan, where stomach cancer appeared to play a large role for the decrease due to improved risk factors (eg smoking, salt intake, and *Helicobacter pylori* infection) and treatment strategies, overall cancer incidence has been continuously increasing.[2]

In Western countries, occupational class, a fundamental proxy for socioeconomic status (SES), is considered as a major determinant of cancer incidence.[3] For example,

stomach and lung cancers tend to show a reduced risk in higher-SES individuals, such as professional and managerial workers.[3] Major lifestyle risk behaviors, such as smoking and alcohol consumption, are thought to underlie the observed socioeconomic gradient in cancer risk.[3] For example, smoking is less prevalent in higher occupational class, and this may account for a lower risk of stomach and lung cancer.[4,5]

In Japan, as well as in other Asian countries, although previous studies investigated the association between occupational class and cancer *mortality* (but not incidence)[6,7] or the ecological association between cancer incidence and *regional-level* SES (but not individual level),[8,9] few studies evaluated the association of occupational class and risk of cancer incidence using individual-level data. Also, the background cancer risks associated with occupational class differ between western and nonwestern contexts. For example, compared with Western countries, the distribution of *H. pylori* infection (stomach cancer risk) is higher in Japan.[2,10] For socioeconomic patterns for other potential cancer risks related to occupation, work-related psychological stress partly differ between these two contexts.[11] In contrast to Western countries, where occupational stress is typically higher among low-occupational classes compared with high-occupational ones, the opposite pattern has been seen in Japan (eg high suicide rate in managerial position).[6,11] Recently, with regard to major cancer incidence among women in Japan, we found a reduced risk of stomach and lung cancer and an excess risk of breast cancer in higher occupational class using individual-level data.[10] However, the association among men remains unclear in Japan. As applying female results to men is inappropriate due to etiology of cancer[12] and distribution of occupational class,[6] it is necessary to determine socioeconomic inequalities in male cancer incidence separately from those with females.

Using a nationwide, multicenter inpatient dataset including individual-level clinical data and occupational information, we examined whether the risk of male cancer incidence is associated with occupational class in Japan. We also determined whether the observed association persists even after controlling for smoking and alcohol consumption.

2 | MATERIALS AND METHODS

2.1 | Study setting

We conducted a multicenter, hospital-based matched case–control study using male inpatient data from the Inpatient Clinico-Occupational Database of Rosai Hospital Group (ICOD-R), run by the Japan Organization of Occupational Health and Safety (JOHAS). Details of ICOD-R have been described elsewhere.[10,11,13-15] Briefly, the Rosai Hospital group consists of 33 general hospitals in main urban areas and rural areas of Japan; it has collected medical chart information confirmed by physicians (including basic socio-demographic characteristics, clinical history, and diagnosis of current and past diseases, pathological information, treatment, and outcome for every inpatient) since 1984. The clinical diagnosis and comorbid diseases, extracted from physicians' medical charts confirmed at discharge, are coded according to the International Classification of Diseases, 9th Revision (ICD-9) or 10th Revision (ICD-10).[10,11,13-15] Although the Rosai Hospitals were initially established by the Ministry of Labour of Japan in 1949 for the working population, the hospital group has since expanded coverage to the general population as well as the working population.[14] The profiles of the patients, including occupational class, are nationally representative.[10,11]

From questionnaires completed at the time of admission, ICOD-R also includes the occupational history of every inpatient (current and three most recent jobs with duration) as well as smoking and alcohol habits (status, daily amount, and duration). Detailed occupational history is coded with the three-digit codes of the standardized national classification, the Japan Standard Occupational Classification and Japan Standard Industrial Classification, corresponding, respectively, to the International Standard Industrial Classification and International Standard Occupational Classification; JOHAS updated the previous job codes to be consistent with changes in coding practice according to the revisions of the standardized national classification.[10,11,13-15] Written informed consent was obtained before patients completed the questionnaires; trained registrars and nurses are in charge of registering the data. The database currently contains data from over 6 million inpatients.

We obtained a de-identified dataset under the research agreement between the authors and JOHAS, and the research ethics committees of The University of Tokyo, Tokyo (Protocol Number 3890-5) and Kanto Rosai Hospital, Kanagawa (Protocol Number 2014-38) approved the study.

2.2 | Cases and controls

The study subjects comprised 1 240 370 subjects (214 123 male cancer cases and their 1 026 247 male hospital controls) aged 20 years and older admitted to the hospital between 1984 and 2016. To select cases and controls from the same source population, we randomly sampled five controls for each cancer case, matched for age, admission date, and admitting hospital.[10,14] The matching process, however, generated less than five controls for some cases.

The cancer cases comprised those patients whose main diagnosis was initial cancer, confirmed by physicians on discharge with their medical chart information, pathological, or imaging information (computed tomography, magnetic resonance imaging, and endoscopy).[10,11,13-15] We defined cancer incidence as the first-time admission to the

hospitals with a cancer diagnosis; the validation for the diagnosis corresponding to ICD-9 or ICD-10 in the database has been described elsewhere.[10,11,13-15] The database is unique to the Rosai Hospital group and so differs from medical claims data, which may have less diagnostic accuracy.[16] Following national statistics in Japan,[1,17,18] we specified the top 10 common male cancer sites: stomach, lung, colorectum, prostate, liver, esophagus, pancreas, bladder, kidney (including pelvis and ureter), and malignant lymphoma (Table S1). Less common cancers were additionally specified. The prevalence of these cancers was mostly identical to that in national statistics, and the total of our male cancer cases amounted ~2% of the total incidence of male cancer in Japan (Table S1).[1,17,18]

Based on a methodology used in previous studies,[10,11] our controls comprised male patients diagnosed with eye and ear disease (ICD-9, 360-389 and ICD-10, H00-H95; 36.5%), genitourinary system disease (ICD-9, 580-629 and ICD-10, N00-N99; 42.9%), infectious and parasitic disease (ICD-9, 1-136 and ICD-10, A00-B99; 13.6%), or skin diseases (ICD-9, 680-709 and ICD-10, L00-L99; 7.0%), which were not linked to occupational class (Figure S1).

2.3 | Occupational class and covariates

To classify occupational class, we chose the longest-held job for each patient from his occupational history (current and three most recent jobs).[10,11] The longest-held occupations were classified into four occupational classes (blue-collar, service, professional, and manager), cross-classified by three industrial clusters (blue-collar industry, service industry, and white-collar industry; Figure S2).[10,11] That is, the blue-collar industry included agriculture, forestry and fisheries, mining and quarrying of stone, construction, manufacturing, electricity, gas, heat supply and water, and transport and postal services; the service industry included wholesale and retail trade, accommodations, eating and drinking services, living-related, personal and amusement services, compound services, and services not elsewhere categorized; and the white-collar industry included information and communications, finance and insurance, real estate, goods rental and leasing, education and learning support, medical, health care and welfare, and government except elsewhere classified.[10,11] The "other" group comprised patients who were not actively engaged in paid employment (unemployed, nonworker, miscellaneous worker, and student) were additionally specified.

Confounding factors included age, admission date, and admitting hospitals, and mediating factors included smoking (log [1 + pack-year]) and alcohol consumption (log [1 + daily gram of ethanol intake]).[10,11,13,14] Drinking habits were assessed prior to symptom onset related to admission.

2.4 | Statistical analysis

Overall one-third of the study subjects had missing data, and excluding those with missing data may lead to biased inference.[11] To deal with missing data, we performed multiple imputation for missing data among 1 240 370 study subjects using all data, including occupational class, smoking, and alcohol consumption.[10,11,19] Five imputed datasets with Multiple Imputation by Chained Equations method were generated.[10,11,19] The following missing data were multiply imputed: occupational class (350 751, 28.3%), smoking (385 511, 31.1%), alcohol consumption (478 059, 38.5%).[10,11]

Next, using blue-collar workers in blue-collar industries as the referent group, odds ratios (ORs), and 95% confidence intervals (CIs) in each occupational class for specific cancer sites and overall cancer incidence were estimated by conditional logistic regression with multiple imputation, matched for age, admission date, and admitting hospital (model 1).[10,11,19] To assess the contribution of major modifiable risk factors, smoking and alcohol consumption were additionally adjusted (model 2).

In sensitivity analyses, based on the distribution of our data and previous studies from ICOD-R, we performed stratified analyses by age (20-64 vs 65 and above) and admission date (1984-2002 vs 2003-2016), respectively.[13,20] In addition, without performing multiple imputation, we performed (a) conditional logistic regression and (b) multilevel logistic regression with random intercepts fitted for each hospital (level 1, individual; level 2, hospital), among patients with complete information (125 342 cases, 559 198 controls). Due to insufficient number of the cases, these analyses were limited to stomach, lung, prostate, and overall cancer. Additionally, using alternative control groups (all available hospital controls diagnosed with benign diseases), we performed conditional logistic regression with multiple imputation for lung cancer (22 086 cases, 110 321 controls) and prostate cancer (28 648 cases, 143 090 controls). Alpha was set at 0.05, and all *P*-values were two-sided. Data were analyzed using STATA/MP13.1 (Stata-Corp LP, College Station, TX).

3 | RESULTS

The mean age [mean (SD)] in the controls and cases was, respectively, 67 (11) years and 67 (11) years. Higher occupational class was clearly associated with reduced risks for stomach and lung cancer. In all three industries, higher occupational class men (professionals and managers) had significantly lower odds ratios for stomach and lung cancer, with the exception of risk for stomach cancer in managers in blue-collar industries (Table 1). Even after fully controlling for smoking and alcohol consumption, the

TABLE 1 Odds ratios of each occupational class associated with risk for top 10 common cancers and overall cancer incidence in Japan

Characteristics	Control, %[a]	Case, %[a]	Model 1 OR (95% CI)[b]	Model 2 OR (95% CI)[b]
Esophagus	n = 30 545	n = 6317		
Occupational class				
Blue-collar industry				
Blue-collar	32.4	34.5	1.00	1.00
Service	11.2	11.4	0.96 (0.87-1.06)	0.95 (0.85-1.05)
Professional	3.3	2.9	0.82 (0.67-0.99)	0.81 (0.66-0.98)
Manager	4.3	4.6	0.99 (0.85-1.16)	0.95 (0.81-1.11)
Service industry				
Blue-collar	3.0	3.1	1.00 (0.83-1.21)	1.03 (0.84-1.24)
Service	10.6	11.2	1.01 (0.91-1.11)	1.02 (0.92-1.13)
Professional	0.9	1.0	1.04 (0.77-1.40)	1.02 (0.75-1.40)
Manager	2.2	2.1	0.91 (0.74-1.13)	0.90 (0.72-1.13)
White-collar industry				
Blue-collar	1.9	2.0	1.00 (0.81-1.25)	1.03 (0.83-1.27)
Service	6.7	5.9	0.83 (0.71-0.95)	0.82 (0.71-0.95)
Professional	4.8	4.0	0.78 (0.66-0.93)	0.82 (0.70-0.97)
Manager	1.4	1.1	0.70 (0.49-0.99)	0.73 (0.52-1.02)
Others				
Others	17.3	16.2	0.86 (0.78-0.94)	0.96 (0.87-1.06)
Smoking, mean[c]	2.31	2.86		1.19 (1.16-1.21)
Alcohol consumption, mean[d]	2.37	3.02		1.29 (1.26-1.33)
Stomach	n = 203 506	n = 42 510		
Occupational class				
Blue-collar industry				
Blue-collar	32.5	35.3	1.00	1.00
Service	10.8	11.0	0.95 (0.90-0.99)	0.94 (0.90-0.99)
Professional	3.0	3.0	0.93 (0.87-0.99)	0.93 (0.87-1.00)
Manager	4.3	4.4	0.95 (0.90-1.02)	0.93 (0.87-0.99)
Service industry				
Blue-collar	2.9	3.0	0.94 (0.86-1.01)	0.94 (0.87-1.02)
Service	10.6	10.3	0.91 (0.87-0.95)	0.91 (0.87-0.95)
Professional	0.9	0.8	0.85 (0.73-0.98)	0.86 (0.74-1.00)
Manager	2.2	2.0	0.86 (0.79-0.94)	0.86 (0.79-0.94)
White-collar industry				
Blue-collar	1.9	1.9	0.92 (0.84-1.01)	0.93 (0.85-1.02)
Service	6.9	6.3	0.84 (0.80-0.89)	0.85 (0.81-0.90)
Professional	5.0	4.2	0.77 (0.72-0.82)	0.80 (0.75-0.86)
Manager	1.5	1.3	0.79 (0.71-0.89)	0.80 (0.72-0.90)
Others				
Others	17.8	16.5	0.83 (0.80-0.86)	0.86 (0.83-0.89)
Smoking, mean[c]	2.26	2.59		1.12 (1.11-1.13)
Alcohol consumption, mean[d]	2.32	2.53		1.06 (1.05-1.07)
Colorectum	n = 128 696	n = 27 074		

(Continues)

TABLE 1 (Continued)

Characteristics	Control, %[a]	Case, %[a]	Model 1 OR (95% CI)[b]	Model 2 OR (95% CI)[b]
Occupational class				
Blue-collar industry				
Blue-collar	31.6	32.3	1.00	1.00
Service	11.5	11.7	1.01 (0.96-1.07)	1.01 (0.96-1.07)
Professional	3.4	3.5	1.02 (0.94-1.12)	1.02 (0.94-1.12)
Manager	4.1	4.0	0.99 (0.92-1.06)	0.97 (0.90-1.04)
Service industry				
Blue-collar	3.0	3.2	1.05 (0.97-1.14)	1.07 (0.98-1.15)
Service	11.0	11.4	1.02 (0.96-1.08)	1.02 (0.96-1.08)
Professional	1.0	0.9	0.91 (0.77-1.09)	0.93 (0.78-1.10)
Manager	2.0	2.1	1.01 (0.91-1.13)	1.01 (0.90-1.13)
White-collar industry				
Blue-collar	1.9	1.8	0.89 (0.77-1.02)	0.89 (0.77-1.02)
Service	7.1	6.9	0.96 (0.89-1.04)	0.97 (0.90-1.04)
Professional	5.1	5.1	0.96 (0.89-1.04)	0.99 (0.92-1.06)
Manager	1.4	1.2	0.88 (0.77-0.99)	0.88 (0.78-1.00)
Others				
Others	17.0	16.1	0.90 (0.85-0.95)	0.94 (0.89-0.99)
Smoking, mean[c]	2.38	2.56		1.06 (1.05-1.07)
Alcohol consumption, mean[d]	2.45	2.67		1.09 (1.08-1.10)
Liver	n = 88 342	n = 18 354		
Occupational class				
Blue-collar industry				
Blue-collar	31.9	32.7	1.00	1.00
Service	11.1	11.6	1.02 (0.96-1.08)	1.02 (0.96-1.08)
Professional	3.1	2.8	0.87 (0.76-0.99)	0.87 (0.76-0.99)
Manager	4.6	5.1	1.09 (1.00-1.19)	1.07 (0.98-1.17)
Service industry				
Blue-collar	2.9	3.1	1.03 (0.93-1.14)	1.04 (0.94-1.15)
Service	10.7	10.6	0.97 (0.91-1.03)	0.97 (0.92-1.03)
Professional	0.8	0.7	0.89 (0.73-1.09)	0.91 (0.75-1.11)
Manager	2.1	2.2	1.01 (0.88-1.16)	1.01 (0.88-1.16)
White-collar industry				
Blue-collar	1.9	1.7	0.84 (0.74-0.96)	0.84 (0.74-0.96)
Service	7.0	6.0	0.84 (0.77-0.92)	0.85 (0.78-0.93)
Professional	4.9	3.7	0.74 (0.67-0.81)	0.76 (0.69-0.84)
Manager	1.6	1.3	0.81 (0.67-0.97)	0.81 (0.68-0.97)
Others				
Others	17.3	18.6	1.04 (0.98-1.10)	1.07 (1.00-1.14)
Smoking, mean[c]	2.28	2.51		1.09 (1.07-1.10)
Alcohol consumption, mean[d]	2.34	2.49		1.04 (1.02-1.05)
Pancreas	n = 23 635	n = 4976		
Occupational class				

(Continues)

TABLE 1 (Continued)

Characteristics	Control, %[a]	Case, %[a]	Model 1 OR (95% CI)[b]	Model 2 OR (95% CI)[b]
Blue-collar industry				
Blue-collar	31.9	33.6	1.00	1.00
Service	10.7	11.7	1.04 (0.93-1.16)	1.03 (0.93-1.15)
Professional	3.1	2.9	0.88 (0.69-1.13)	0.89 (0.70-1.13)
Manager	4.4	4.4	0.96 (0.80-1.16)	0.95 (0.79-1.14)
Service industry				
Blue-collar	3.1	3.2	0.99 (0.80-1.22)	1.01 (0.82-1.24)
Service	10.5	10.2	0.92 (0.77-1.11)	0.93 (0.77-1.12)
Professional	0.9	0.9	0.92 (0.62-1.39)	0.93 (0.62-1.40)
Manager	2.1	2.2	1.00 (0.79-1.27)	1.00 (0.79-1.27)
White-collar industry				
Blue-collar	2.0	1.6	0.75 (0.58-0.98)	0.76 (0.58-0.99)
Service	6.7	5.9	0.83 (0.72-0.96)	0.84 (0.73-0.96)
Professional	4.8	4.5	0.90 (0.75-1.07)	0.93 (0.78-1.11)
Manager	1.5	1.3	0.83 (0.62-1.11)	0.85 (0.63-1.14)
Others				
Others	18.2	17.6	0.88 (0.80-0.97)	0.91 (0.83-1.01)
Smoking, mean[c]	2.28	2.61		1.14 (1.11-1.17)
Alcohol consumption, mean[d]	2.33	2.41		1.00 (0.98-1.03)
Lung	n = 104 064	n = 21 922		
Occupational class				
Blue-collar industry				
Blue-collar	32.6	37.5	1.00	1.00
Service	10.6	10.6	0.87 (0.83-0.93)	0.86 (0.82-0.91)
Professional	3.1	2.7	0.75 (0.68-0.84)	0.76 (0.68-0.85)
Manager	4.0	3.9	0.86 (0.79-0.93)	0.83 (0.76-0.90)
Service industry				
Blue-collar	2.8	2.9	0.89 (0.81-0.98)	0.89 (0.81-0.98)
Service	10.0	9.4	0.82 (0.77-0.87)	0.83 (0.78-0.89)
Professional	0.9	0.7	0.65 (0.54-0.77)	0.68 (0.56-0.82)
Manager	2.0	1.9	0.80 (0.71-0.90)	0.81 (0.72-0.92)
White-collar industry				
Blue-collar	1.7	1.5	0.76 (0.66-0.88)	0.79 (0.69-0.91)
Service	6.3	5.4	0.75 (0.68-0.82)	0.77 (0.70-0.84)
Professional	4.6	3.2	0.61 (0.55-0.66)	0.66 (0.60-0.73)
Manager	1.4	1.0	0.61 (0.51-0.72)	0.66 (0.55-0.79)
Others				
Others	19.8	19.2	0.82 (0.79-0.86)	0.90 (0.86-0.95)
Smoking, mean[c]	2.33	3.04		1.36 (1.35-1.38)
Alcohol consumption, mean[d]	2.31	2.43		0.99 (0.98-1.00)
Prostate	n = 136 573	n = 28 392		
Occupational class				
Blue-collar industry				

(Continues)

TABLE 1 (Continued)

Characteristics	Control, %[a]	Case, %[a]	Model 1 OR (95% CI)[b]	Model 2 OR (95% CI)[b]
Blue-collar	31.5	31.8	1.00	1.00
Service	11.4	12.0	1.06 (1.01-1.12)	1.06 (1.01-1.12)
Professional	3.5	3.6	1.06 (0.99-1.15)	1.06 (0.98-1.14)
Manager	3.9	3.9	1.02 (0.94-1.10)	1.02 (0.94-1.10)
Service industry				
Blue-collar	3.0	2.7	0.90 (0.82-0.99)	0.91 (0.83-0.99)
Service	10.4	10.1	0.97 (0.91-1.03)	0.97 (0.91-1.03)
Professional	1.1	1.1	0.98 (0.86-1.11)	0.98 (0.86-1.11)
Manager	2.1	2.0	0.96 (0.86-1.06)	0.96 (0.86-1.06)
White-collar industry				
Blue-collar	1.9	2.0	1.07 (0.96-1.20)	1.07 (0.95-1.19)
Service	6.5	6.7	1.03 (0.97-1.10)	1.03 (0.97-1.10)
Professional	4.9	5.4	1.10 (1.03-1.18)	1.10 (1.03-1.18)
Manager	1.2	1.3	1.07 (0.94-1.22)	1.07 (0.93-1.22)
Others				
Others	18.5	17.3	0.90 (0.86-0.94)	0.90 (0.86-0.94)
Smoking, mean[c]	2.41	2.37		0.98 (0.97-0.99)
Alcohol consumption, mean[d]	2.36	2.43		1.03 (1.02-1.05)
Kidney, pelvis and ureter	n = 26 900	n = 5552		
Occupational class				
Blue-collar industry				
Blue-collar	31.4	31.4	1.00	1.00
Service	11.9	12.1	1.03 (0.93-1.14)	1.03 (0.93-1.14)
Professional	3.8	3.8	1.04 (0.81-1.35)	1.05 (0.81-1.36)
Manager	4.0	4.7	1.19 (1.02-1.39)	1.17 (1.00-1.37)
Service industry				
Blue-collar	2.9	3.1	1.07 (0.87-1.32)	1.08 (0.87-1.33)
Service	11.0	10.8	0.99 (0.88-1.11)	0.99 (0.88-1.11)
Professional	0.9	1.0	1.17 (0.81-1.67)	1.17 (0.82-1.67)
Manager	2.0	2.3	1.15 (0.93-1.42)	1.15 (0.92-1.42)
White-collar industry				
Blue-collar	2.1	1.7	0.84 (0.65-1.09)	0.84 (0.65-1.10)
Service	7.2	7.3	1.02 (0.88-1.17)	1.03 (0.89-1.18)
Professional	5.3	5.4	1.04 (0.88-1.22)	1.07 (0.90-1.26)
Manager	1.4	1.4	0.97 (0.72-1.29)	0.97 (0.73-1.30)
Others				
Others	16.1	15.1	0.93 (0.82-1.04)	0.95 (0.85-1.07)
Smoking, mean[c]	2.35	2.58		1.08 (1.06-1.11)
Alcohol consumption, mean[d]	2.41	2.58		1.05 (1.03-1.08)
Bladder	n = 64 871	n = 13 590		
Occupational class				
Blue-collar industry				
Blue-collar	31.3	32.8	1.00	1.00

(Continues)

TABLE 1 (Continued)

Characteristics	Control, %[a]	Case, %[a]	Model 1 OR (95% CI)[b]	Model 2 OR (95% CI)[b]
Service	10.6	11.6	1.06 (0.98-1.15)	1.05 (0.97-1.14)
Professional	3.2	3.0	0.91 (0.80-1.03)	0.90 (0.79-1.03)
Manager	4.3	4.6	1.05 (0.95-1.16)	1.02 (0.92-1.13)
Service industry				
Blue-collar	2.9	2.7	0.90 (0.79-1.03)	0.90 (0.78-1.03)
Service	10.1	10.4	0.99 (0.93-1.06)	1.00 (0.93-1.07)
Professional	0.9	1.0	1.14 (0.93-1.39)	1.14 (0.92-1.40)
Manager	2.1	2.2	1.02 (0.88-1.18)	1.02 (0.88-1.19)
White-collar industry				
Blue-collar	1.8	1.6	0.89 (0.76-1.03)	0.89 (0.77-1.04)
Service	6.7	5.9	0.84 (0.75-0.95)	0.85 (0.76-0.95)
Professional	4.9	4.5	0.88 (0.78-0.98)	0.92 (0.82-1.02)
Manager	1.4	1.2	0.78 (0.62-0.98)	0.78 (0.63-0.98)
Others				
Others	19.9	18.4	0.86 (0.81-0.91)	0.89 (0.84-0.94)
Smoking, mean[c]	2.29	2.69		1.17 (1.15-1.18)
Alcohol consumption, mean[d]	2.31	2.43		1.02 (1.00-1.03)
Malignant lymphoma	n = 29 528	n = 6157		
Occupational class				
Blue-collar industry				
Blue-collar	31.0	33.4	1.00	1.00
Service	11.7	11.5	0.92 (0.83-1.02)	0.92 (0.83-1.01)
Professional	3.8	3.4	0.82 (0.69-0.96)	0.82 (0.70-0.97)
Manager	3.8	3.9	0.96 (0.76-1.21)	0.95 (0.75-1.20)
Service industry				
Blue-collar	3.1	3.8	1.14 (0.97-1.34)	1.14 (0.97-1.33)
Service	11.0	10.1	0.86 (0.77-0.96)	0.86 (0.77-0.96)
Professional	0.9	1.0	0.94 (0.68-1.30)	0.94 (0.69-1.30)
Manager	1.9	1.9	0.92 (0.69-1.22)	0.92 (0.69-1.21)
White-collar industry				
Blue-collar	2.0	1.8	0.82 (0.65-1.04)	0.83 (0.65-1.04)
Service	7.5	6.9	0.86 (0.75-0.98)	0.86 (0.76-0.98)
Professional	5.5	5.1	0.85 (0.72-1.01)	0.87 (0.73-1.03)
Manager	1.4	1.2	0.85 (0.60-1.19)	0.85 (0.61-1.20)
Others				
Others	16.4	16.2	0.90 (0.82-0.99)	0.91 (0.83-1.00)
Smoking, mean[c]	2.30	2.44		1.06 (1.03-1.09)
Alcohol consumption, mean[d]	2.39	2.40		0.99 (0.97-1.02)
All sites	n = 1 026 247	n = 214 123		
Occupational class				
Blue-collar industry				
Blue-collar	31.8	33.6	1.00	1.00
Service	11.1	11.4	0.99 (0.97-1.00)	0.98 (0.96-1.00)

(Continues)

TABLE 1 (Continued)

Characteristics	Control, %[a]	Case, %[a]	Model 1 OR (95% CI)[b]	Model 2 OR (95% CI)[b]
Professional	3.3	3.1	0.92 (0.88-0.96)	0.92 (0.88-0.96)
Manager	4.2	4.3	0.98 (0.96-1.01)	0.97 (0.94-0.99)
Service industry				
Blue-collar	2.9	3.0	0.97 (0.94-1.00)	0.97 (0.94-1.00)
Service	10.6	10.6	0.95 (0.93-0.96)	0.95 (0.94-0.97)
Professional	0.9	0.9	0.92 (0.86-0.98)	0.93 (0.87-1.00)
Manager	2.1	2.0	0.93 (0.89-0.97)	0.93 (0.89-0.97)
White-collar industry				
Blue-collar	1.9	1.8	0.90 (0.86-0.94)	0.90 (0.86-0.95)
Service	6.9	6.3	0.88 (0.86-0.90)	0.89 (0.86-0.91)
Professional	5.0	4.5	0.86 (0.83-0.88)	0.89 (0.86-0.92)
Manager	1.4	1.2	0.82 (0.78-0.86)	0.83 (0.79-0.87)
Others				
Others	17.9	17.3	0.89 (0.88-0.91)	0.92 (0.91-0.94)
Smoking, mean[c]	2.31	2.58		1.10 (1.10-1.11)
Alcohol consumption, mean[d]	2.35	2.51		1.05 (1.04-1.05)

CI, confidence interval; OR, odds ratio.

[a]Data were estimated with five imputed datasets. Percentages may not total 100 because of rounding with multiple imputation.

[b]Conditional logistic regression with multiple imputation, matched for age, admission date, and admitting hospital (model 1); additional adjustment for smoking and alcohol consumption (model 2).

[c]Log (1 + pack-year).

[d]Log (1 + daily gram of ethanol intake).

observed lower odds in higher occupational class across all industries were not attenuated and remained significantly associated with stomach cancer (adjusted OR ranged from 0.80 for managers in white-collar industries to 0.93 for professionals in blue-collar industries) and lung cancer (adjusted OR ranged from 0.66 for managers in white-collar industries to 0.83 for managers in blue-collar industries; model 2, Table 1). Additionally, service workers in all industries and blue-collar workers in service and white-collar industries also had significantly lower odds ratios for lung cancer.

Among the remainder of the top 10 common cancers, higher occupational class in white-collar industries was associated with reduced risks for liver, esophagus, and bladder cancer, as well as malignant lymphoma (Table 1). Higher occupational class tended to be associated with potentially lower risk for pancreatic cancer (although not statistically significant), while occupational class was not clearly associated with colorectal cancer risk (Table 1). By contrast, an excess cancer risk was associated with professionals in white-collar industries for prostate cancer, as well as a tendency of excess risk with higher occupational class in blue-collar industries was observed for kidney cancer (Table 1). As a whole, a reduced risk was associated with higher occupational class for overall cancer incidence (Table 1).

Some less common cancers (such as gallbladder and bile duct cancer, leukemia, and multiple myeloma) appeared to hint at a reduced risk with higher occupational class (Table S2). The results of sensitivity analyses showed almost the same occupational gradient patterns as seen in the main result (Tables 2 and 3; Table S3 and Figure S3).

4 | DISCUSSION

4.1 | All cancer sites

In Western countries, overall male cancer incidence has shown a slightly inverse socioeconomic gradient (reduced risk with higher occupational class).[3] Focusing on the odds ratios for cancer incidence in higher-SES groups (ie managers and professionals) across industrial clusters, we observed an inverse socioeconomic gradient in Japan, explained by reduced incidence among higher occupational class groups for stomach, lung, liver, esophagus, and bladder cancer, as well as malignant lymphoma.

4.2 | Inverse occupational gradient

Although smoking and alcohol consumption may substantially mediate the inverse socioeconomic gradient for

TABLE 2 Odds ratios of each occupational class associated with risk for stomach, lung, prostate, and overall cancer incidence stratified by age

Occupational class	Control, %[a]	Case, %[a]	Model 1 OR (95% CI)[b]	Model 2 OR (95% CI)[b]
Stomach				
Age 20-64	n = 82 294	n = 16 925		
Blue-collar industry				
Blue-collar	32.6	35.9	1.00	1.00
Service	12.4	12.6	0.97 (0.92-1.02)	0.96 (0.91-1.02)
Professional	3.7	3.8	0.93 (0.83-1.04)	0.93 (0.83-1.04)
Manager	4.6	4.9	0.95 (0.87-1.02)	0.93 (0.86-1.00)
Service industry				
Blue-collar	3.6	3.5	0.99 (0.89-1.10)	0.99 (0.89-1.10)
Service	12.9	12.9	0.90 (0.85-0.95)	0.90 (0.85-0.96)
Professional	0.7	0.6	0.90 (0.76-1.06)	0.91 (0.77-1.08)
Manager	2.1	2.0	0.86 (0.77-0.96)	0.87 (0.77-0.97)
White-collar industry				
Blue-collar	2.3	2.4	0.88 (0.79-0.99)	0.90 (0.81-1.01)
Service	8.8	8.2	0.84 (0.78-0.91)	0.84 (0.78-0.91)
Professional	5.7	4.7	0.79 (0.73-0.85)	0.82 (0.76-0.88)
Manager	1.6	1.5	0.75 (0.65-0.87)	0.76 (0.66-0.88)
Others				
Others	9.0	6.9	0.87 (0.83-0.91)	0.90 (0.86-0.94)
Age 65 and above	n = 121 212	n = 25 585		
Blue-collar industry				
Blue-collar	32.4	35.0	1.00	1.00
Service	9.6	10.0	0.92 (0.86-0.99)	0.91 (0.85-0.98)
Professional	2.5	2.5	0.92 (0.84-1.01)	0.93 (0.84-1.02)
Manager	4.0	4.1	0.96 (0.88-1.05)	0.93 (0.85-1.01)
Service industry				
Blue-collar	2.4	2.6	0.88 (0.79-0.99)	0.89 (0.80-1.00)
Service	9.0	8.6	0.91 (0.86-0.97)	0.91 (0.86-0.97)
Professional	0.9	0.9	0.76 (0.58-0.99)	0.78 (0.59-1.02)
Manager	2.2	2.0	0.86 (0.76-0.99)	0.85 (0.74-0.97)
White-collar industry				
Blue-collar	1.7	1.6	0.95 (0.82-1.11)	0.96 (0.82-1.11)
Service	5.6	5.1	0.84 (0.78-0.90)	0.86 (0.80-0.92)
Professional	4.4	3.8	0.74 (0.67-0.83)	0.78 (0.70-0.87)
Manager	1.4	1.1	0.84 (0.73-0.98)	0.85 (0.73-0.99)
Others				
Others	23.8	22.8	0.69 (0.63-0.75)	0.73 (0.67-0.80)
Lung				
Age 20-64	n = 28 411	n = 5893		
Blue-collar industry				
Blue-collar	32.6	35.9	1.00	1.00
Service	12.4	12.6	0.90 (0.84-0.97)	0.89 (0.83-0.95)

(Continues)

TABLE 2 (Continued)

Occupational class	Control, %[a]	Case, %[a]	Model 1 OR (95% CI)[b]	Model 2 OR (95% CI)[b]
Professional	3.7	3.8	0.81 (0.72-0.92)	0.81 (0.72-0.91)
Manager	4.6	4.9	0.89 (0.80-0.98)	0.86 (0.77-0.95)
Service industry				
Blue-collar	3.6	3.5	0.93 (0.83-1.05)	0.92 (0.82-1.03)
Service	12.9	12.9	0.83 (0.76-0.89)	0.84 (0.77-0.91)
Professional	0.7	0.6	0.63 (0.51-0.78)	0.65 (0.52-0.82)
Manager	2.1	2.0	0.81 (0.70-0.93)	0.82 (0.71-0.96)
White-collar industry				
Blue-collar	2.3	2.4	0.81 (0.68-0.96)	0.85 (0.71-1.02)
Service	8.8	8.2	0.75 (0.68-0.84)	0.76 (0.69-0.85)
Professional	5.7	4.7	0.62 (0.55-0.70)	0.68 (0.60-0.76)
Manager	1.6	1.5	0.65 (0.52-0.81)	0.70 (0.56-0.89)
Others				
Others	9.0	6.9	0.84 (0.80-0.88)	0.92 (0.87-0.97)
Age 65 and above	n = 75 653	n = 16 029		
Blue-collar industry				
Blue-collar	32.4	35.0	1.00	1.00
Service	9.6	10.0	0.82 (0.73-0.91)	0.81 (0.72-0.91)
Professional	2.5	2.5	0.65 (0.54-0.78)	0.67 (0.55-0.80)
Manager	4.0	4.1	0.78 (0.66-0.94)	0.76 (0.64-0.91)
Service industry				
Blue-collar	2.4	2.6	0.80 (0.68-0.94)	0.82 (0.70-0.97)
Service	9.0	8.6	0.80 (0.72-0.88)	0.80 (0.72-0.88)
Professional	0.9	0.9	0.71 (0.48-1.03)	0.76 (0.52-1.12)
Manager	2.2	2.0	0.78 (0.63-0.97)	0.78 (0.62-0.98)
White-collar industry				
Blue-collar	1.7	1.6	0.67 (0.51-0.87)	0.67 (0.51-0.88)
Service	5.6	5.1	0.74 (0.65-0.84)	0.77 (0.67-0.87)
Professional	4.4	3.8	0.57 (0.48-0.67)	0.63 (0.53-0.74)
Manager	1.4	1.1	0.52 (0.34-0.80)	0.55 (0.36-0.85)
Others				
Others	23.8	22.8	0.77 (0.69-0.87)	0.86 (0.76-0.97)
Prostate				
Age 20-64	n = 25 068	n = 5117		
Blue-collar industry				
Blue-collar	32.6	35.9	1.00	1.00
Service	12.4	12.6	1.06 (1.00-1.13)	1.06 (1.00-1.12)
Professional	3.7	3.8	1.00 (0.92-1.10)	1.00 (0.91-1.10)
Manager	4.6	4.9	1.01 (0.92-1.10)	1.00 (0.92-1.10)
Service industry				
Blue-collar	3.6	3.5	0.92 (0.83-1.02)	0.92 (0.83-1.03)
Service	12.9	12.9	0.97 (0.91-1.03)	0.97 (0.91-1.03)
Professional	0.7	0.6	0.99 (0.86-1.14)	0.99 (0.87-1.14)

(Continues)

TABLE 2 (Continued)

Occupational class	Control, %[a]	Case, %[a]	Model 1 OR (95% CI)[b]	Model 2 OR (95% CI)[b]
Manager	2.1	2.0	0.90 (0.81-1.01)	0.90 (0.81-1.01)
White-collar industry				
Blue-collar	2.3	2.4	1.02 (0.90-1.16)	1.02 (0.90-1.15)
Service	8.8	8.2	0.97 (0.90-1.05)	0.97 (0.90-1.05)
Professional	5.7	4.7	1.03 (0.96-1.11)	1.03 (0.96-1.11)
Manager	1.6	1.5	1.03 (0.89-1.19)	1.03 (0.89-1.19)
Others				
Others	9.0	6.9	0.91 (0.86-0.95)	0.91 (0.86-0.95)
Age 65 and above	n = 111 505	n = 23 275		
Blue-collar industry				
Blue-collar	32.4	35.0	1.00	1.00
Service	9.6	10.0	1.07 (0.96-1.19)	1.08 (0.96-1.20)
Professional	2.5	2.5	1.27 (1.09-1.47)	1.26 (1.08-1.47)
Manager	4.0	4.1	1.07 (0.91-1.26)	1.07 (0.91-1.26)
Service industry				
Blue-collar	2.4	2.6	0.86 (0.71-1.04)	0.86 (0.70-1.04)
Service	9.0	8.6	1.00 (0.90-1.11)	1.01 (0.90-1.12)
Professional	0.9	0.9	0.88 (0.56-1.38)	0.87 (0.56-1.37)
Manager	2.2	2.0	1.22 (0.99-1.51)	1.23 (0.99-1.52)
White-collar industry				
Blue-collar	1.7	1.6	1.26 (1.03-1.55)	1.26 (1.03-1.54)
Service	5.6	5.1	1.25 (1.12-1.40)	1.25 (1.11-1.40)
Professional	4.4	3.8	1.41 (1.22-1.62)	1.39 (1.21-1.60)
Manager	1.4	1.1	1.25 (0.96-1.62)	1.24 (0.95-1.61)
Others				
Others	23.8	22.8	0.78 (0.68-0.89)	0.78 (0.68-0.89)
All sites				
Age 20-64	n = 374 853	n = 77 173		
Blue-collar industry				
Blue-collar	31.6	33.4	1.00	1.00
Service	12.8	13.1	1.00 (0.98-1.02)	0.99 (0.97-1.02)
Professional	4.2	4.0	0.93 (0.89-0.98)	0.93 (0.89-0.97)
Manager	4.5	4.5	0.99 (0.96-1.03)	0.97 (0.94-1.01)
Service industry				
Blue-collar	3.6	3.7	0.98 (0.93-1.02)	0.98 (0.93-1.02)
Service	13.1	13.3	0.94 (0.92-0.96)	0.95 (0.93-0.97)
Professional	0.7	0.8	0.90 (0.84-0.96)	0.91 (0.85-0.98)
Manager	2.1	2.1	0.92 (0.87-0.97)	0.92 (0.87-0.97)
White-collar industry				
Blue-collar	2.3	2.2	0.90 (0.85-0.95)	0.90 (0.85-0.96)
Service	8.9	8.4	0.86 (0.84-0.89)	0.87 (0.84-0.89)
Professional	5.9	5.3	0.87 (0.83-0.90)	0.89 (0.86-0.93)
Manager	1.6	1.4	0.80 (0.74-0.87)	0.81 (0.75-0.88)

(Continues)

TABLE 2 (Continued)

Occupational class	Control, %[a]	Case, %[a]	Model 1 OR (95% CI)[b]	Model 2 OR (95% CI)[b]
Others				
Others	8.7	8.0	0.90 (0.88-0.92)	0.93 (0.91-0.95)
Age 65 and above	n = 651 394	n = 136 950		
Blue-collar industry				
Blue-collar	32.0	33.7	1.00	1.00
Service	10.1	10.5	0.97 (0.94-1.00)	0.96 (0.93-0.99)
Professional	2.8	2.7	0.90 (0.85-0.96)	0.91 (0.85-0.97)
Manager	4.0	4.1	0.97 (0.92-1.02)	0.95 (0.90-1.00)
Service industry				
Blue-collar	2.5	2.6	0.95 (0.91-1.00)	0.97 (0.92-1.01)
Service	9.2	9.0	0.96 (0.93-0.98)	0.96 (0.94-0.99)
Professional	1.0	0.9	0.96 (0.86-1.07)	0.98 (0.88-1.10)
Manager	2.1	2.0	0.95 (0.90-1.01)	0.95 (0.89-1.01)
White-collar industry				
Blue-collar	1.7	1.6	0.90 (0.84-0.96)	0.90 (0.84-0.97)
Service	5.7	5.1	0.90 (0.86-0.94)	0.91 (0.87-0.96)
Professional	4.5	4.1	0.85 (0.81-0.89)	0.88 (0.85-0.92)
Manager	1.3	1.1	0.84 (0.78-0.91)	0.84 (0.78-0.91)
Others				
Others	23.2	22.5	0.86 (0.83-0.90)	0.91 (0.87-0.95)

CI, confidence interval; OR, odds ratio.

[a]Data were estimated with five imputed datasets. Percentages may not total 100 because of rounding with multiple imputation.

[b]Conditional logistic regression with multiple imputation, matched for age, admission date, and admitting hospital (model 1); additional adjustment for smoking and alcohol consumption (model 2).

stomach and lung cancer in Western countries,[3,4,21] controlling for these behaviors did not fully explain the inverse gradients in the present study. This pattern concurs with the inverse socioeconomic gradient for female stomach and lung cancer incidence in Japan we found in a previous study (eg ORs for managers in blue-collar industries were 0.67 for stomach cancer and 0.40 for lung cancer).[10] Therefore, irrespective of sex differences, other factors, such as dietary habits (high salt diet) and *H. pylori* infection for stomach cancer and occupational/industrial differences in environmental exposure for lung cancer, may play a role.[10,22] Indeed, blue-collar workers in white-collar industries, as well as service workers in all industrial clusters, showed lower odds ratios for lung cancer risk compared with blue-collar workers in blue-collar industries, which also suggests the occupational and industrial differences in environmental exposure to unknown hazardous substance and/or to passive smoking in the workplace linked to lung cancer risk.

Studies in western settings have found an inverse socioeconomic gradient for esophagus cancer (as we did), while gradients for liver and pancreas cancer have been less clear.[3,4,21] We observed a reduced risk with higher occupational class for esophagus and liver cancer, as well as a potentially lower risk among higher-status occupations for pancreas cancer, even after controlling for behavioral risk factors. Dietary habits (vegetables and fruits) may be associated with a reduced risk for these cancers; however, the protective effect remains controversial in the Japanese population.[23] As we observed a reduced liver cancer risk not only in high-occupational class but also in white-collar industries regardless of occupational class, socioeconomic disparities in *Hepatitis C* infection may additionally contribute to the observed socioeconomic gradients in liver cancer.[4] A socioeconomic gradient for bladder cancer and malignant lymphoma has not been consistently observed in Western countries,[3] while we found an inverse socioeconomic gradient. Our findings may be attributable to exposure to aromatic amines in certain high-risk occupation (for bladder cancer)[13,14] as well as the use of pesticides (in the case of malignant lymphoma).[24] Among women in Japan, a socioeconomic gradient was not observed for esophagus, liver, pancreas, bladder cancer, and malignant lymphoma.[10] These differences between men and women regarding socioeconomic patterns may imply a possible sex difference in occupational roles in the same job category[19]; however, other relevant reasons remain unclear.

TABLE 3 Odds ratios of each occupational class associated with risk for stomach, lung, prostate, and overall cancer incidence stratified by admission date

Occupational class	Control, %[a]	Case, %[a]	Model 1 OR (95% CI)[b]	Model 2 OR (95% CI)[b]
Stomach				
Before 2003	n = 120 886	n = 25 081		
Blue-collar industry				
Blue-collar	33.4	35.8	1.00	1.00
Service	9.8	9.9	0.94 (0.89-1.00)	0.93 (0.88-0.99)
Professional	2.4	2.4	0.91 (0.82-1.00)	0.90 (0.82-1.00)
Manager	4.7	5.0	0.88 (0.79-0.98)	0.85 (0.76-0.94)
Service industry				
Blue-collar	2.7	2.6	0.95 (0.86-1.05)	0.96 (0.86-1.06)
Service	9.9	9.8	0.88 (0.83-0.94)	0.88 (0.82-0.94)
Professional	0.6	0.6	0.81 (0.67-0.97)	0.83 (0.68-1.00)
Manager	2.3	2.3	0.77 (0.65-0.92)	0.76 (0.63-0.90)
White-collar industry				
Blue-collar	1.9	1.8	0.93 (0.81-1.05)	0.93 (0.81-1.06)
Service	6.7	6.0	0.85 (0.78-0.93)	0.85 (0.78-0.93)
Professional	4.7	4.1	0.72 (0.66-0.79)	0.76 (0.69-0.83)
Manager	1.7	1.6	0.66 (0.53-0.81)	0.67 (0.54-0.82)
Others				
Others	19.2	18.2	0.77 (0.72-0.83)	0.82 (0.77-0.87)
After 2003	n = 82 620	n = 17 429		
Blue-collar industry				
Blue-collar	31.1	34.7	1.00	1.00
Service	12.2	12.7	0.95 (0.87-1.03)	0.94 (0.87-1.02)
Professional	3.8	3.8	0.94 (0.85-1.04)	0.95 (0.86-1.04)
Manager	3.7	3.5	1.00 (0.93-1.08)	0.98 (0.91-1.05)
Service industry				
Blue-collar	3.2	3.4	0.92 (0.81-1.04)	0.93 (0.82-1.05)
Service	11.5	11.2	0.92 (0.87-0.97)	0.93 (0.88-0.98)
Professional	1.2	1.0	0.89 (0.71-1.10)	0.90 (0.72-1.13)
Manager	2.0	1.7	0.92 (0.82-1.02)	0.92 (0.83-1.03)
White-collar industry				
Blue-collar	2.0	2.0	0.91 (0.78-1.06)	0.93 (0.80-1.08)
Service	7.2	6.8	0.84 (0.78-0.90)	0.85 (0.79-0.91)
Professional	5.3	4.3	0.81 (0.74-0.88)	0.84 (0.77-0.91)
Manager	1.2	0.9	0.87 (0.77-0.98)	0.87 (0.78-0.99)
Others				
Others	15.7	14.0	0.86 (0.82-0.91)	0.89 (0.84-0.94)
Lung				
Before 2003	n = 50 718	n = 10 614		
Blue-collar industry				
Blue-collar	33.4	35.8	1.00	1.00
Service	9.8	9.9	0.87 (0.82-0.94)	0.85 (0.80-0.92)

(Continues)

TABLE 3 (Continued)

Occupational class	Control, %[a]	Case, %[a]	Model 1 OR (95% CI)[b]	Model 2 OR (95% CI)[b]
Professional	2.4	2.4	0.72 (0.62-0.84)	0.72 (0.62-0.85)
Manager	4.7	5.0	0.81 (0.70-0.92)	0.76 (0.66-0.88)
Service industry				
Blue-collar	2.7	2.6	0.87 (0.77-0.99)	0.86 (0.75-0.98)
Service	9.9	9.8	0.79 (0.72-0.87)	0.79 (0.72-0.87)
Professional	0.6	0.6	0.59 (0.47-0.74)	0.62 (0.49-0.78)
Manager	2.3	2.3	0.65 (0.54-0.77)	0.63 (0.53-0.76)
White-collar industry				
Blue-collar	1.9	1.8	0.71 (0.59-0.85)	0.72 (0.60-0.88)
Service	6.7	6.0	0.74 (0.66-0.83)	0.75 (0.67-0.85)
Professional	4.7	4.1	0.54 (0.47-0.62)	0.61 (0.52-0.71)
Manager	1.7	1.6	0.55 (0.42-0.70)	0.62 (0.48-0.80)
Others				
Others	19.2	18.2	0.73 (0.68-0.79)	0.82 (0.76-0.89)
After 2003	n = 53 346	n = 11 308		
Blue-collar industry				
Blue-collar	31.1	34.7	1.00	1.00
Service	12.2	12.7	0.86 (0.78-0.96)	0.86 (0.77-0.95)
Professional	3.8	3.8	0.80 (0.67-0.95)	0.80 (0.67-0.96)
Manager	3.7	3.5	0.91 (0.81-1.01)	0.89 (0.80-1.00)
Service industry				
Blue-collar	3.2	3.4	0.90 (0.76-1.06)	0.91 (0.77-1.07)
Service	11.5	11.2	0.85 (0.77-0.93)	0.87 (0.79-0.95)
Professional	1.2	1.0	0.74 (0.55-0.99)	0.77 (0.57-1.03)
Manager	2.0	1.7	0.96 (0.82-1.13)	1.00 (0.85-1.17)
White-collar industry				
Blue-collar	2.0	2.0	0.82 (0.67-1.01)	0.86 (0.70-1.05)
Service	7.2	6.8	0.76 (0.67-0.86)	0.78 (0.69-0.88)
Professional	5.3	4.3	0.69 (0.60-0.79)	0.74 (0.64-0.84)
Manager	1.2	0.9	0.66 (0.53-0.83)	0.70 (0.55-0.88)
Others				
Others	15.7	14.0	0.92 (0.86-0.98)	0.98 (0.92-1.05)
Prostate				
Before 2003	n = 40 290	n = 8444		
Blue-collar industry				
Blue-collar	33.4	35.8	1.00	1.00
Service	9.8	9.9	1.06 (1.00-1.12)	1.06 (1.00-1.12)
Professional	2.4	2.4	1.12 (1.03-1.22)	1.12 (1.03-1.21)
Manager	4.7	5.0	1.02 (0.93-1.12)	1.02 (0.93-1.12)
Service industry				
Blue-collar	2.7	2.6	0.89 (0.80-1.00)	0.89 (0.80-1.00)
Service	9.9	9.8	0.97 (0.90-1.04)	0.97 (0.90-1.04)
Professional	0.6	0.6	0.91 (0.78-1.05)	0.91 (0.78-1.05)

(Continues)

TABLE 3 (Continued)

Occupational class	Control, %[a]	Case, %[a]	Model 1 OR (95% CI)[b]	Model 2 OR (95% CI)[b]
Manager	2.3	2.3	0.88 (0.77-1.00)	0.88 (0.77-1.00)
White-collar industry				
Blue-collar	1.9	1.8	1.07 (0.92-1.24)	1.06 (0.91-1.23)
Service	6.7	6.0	1.07 (0.99-1.15)	1.06 (0.99-1.14)
Professional	4.7	4.1	1.09 (1.01-1.18)	1.08 (1.00-1.17)
Manager	1.7	1.6	1.12 (0.95-1.32)	1.12 (0.95-1.32)
Others				
Others	19.2	18.2	0.88 (0.83-0.93)	0.88 (0.83-0.93)
After 2003	n = 96 283	n = 19 948		
Blue-collar industry				
Blue-collar	31.1	34.7	1.00	1.00
Service	12.2	12.7	1.06 (0.97-1.17)	1.06 (0.97-1.17)
Professional	3.8	3.8	0.84 (0.71-1.00)	0.84 (0.71-1.01)
Manager	3.7	3.5	1.00 (0.87-1.16)	1.00 (0.87-1.15)
Service industry				
Blue-collar	3.2	3.4	0.94 (0.77-1.15)	0.94 (0.77-1.15)
Service	11.5	11.2	0.98 (0.88-1.08)	0.98 (0.88-1.08)
Professional	1.2	1.0	1.25 (0.91-1.71)	1.25 (0.91-1.71)
Manager	2.0	1.7	1.12 (0.95-1.31)	1.12 (0.95-1.32)
White-collar industry				
Blue-collar	2.0	2.0	1.08 (0.87-1.34)	1.08 (0.87-1.34)
Service	7.2	6.8	0.93 (0.80-1.08)	0.93 (0.80-1.08)
Professional	5.3	4.3	1.14 (1.01-1.29)	1.15 (1.02-1.29)
Manager	1.2	0.9	0.99 (0.80-1.23)	0.99 (0.80-1.23)
Others				
Others	15.7	14.0	0.94 (0.87-1.01)	0.94 (0.87-1.01)
All sites				
Before 2003	n = 523 818	n = 108 858		
Blue-collar industry				
Blue-collar	32.7	33.9	1.00	1.00
Service	9.9	10.0	0.98 (0.96-1.00)	0.97 (0.95-1.00)
Professional	2.6	2.4	0.92 (0.87-0.96)	0.92 (0.87-0.96)
Manager	4.7	4.9	0.94 (0.90-0.98)	0.92 (0.88-0.96)
Service industry				
Blue-collar	2.6	2.6	0.98 (0.94-1.02)	0.98 (0.94-1.02)
Service	9.9	9.8	0.93 (0.91-0.95)	0.93 (0.91-0.95)
Professional	0.6	0.7	0.84 (0.78-0.90)	0.85 (0.80-0.92)
Manager	2.2	2.4	0.83 (0.78-0.89)	0.82 (0.77-0.88)
White-collar industry				
Blue-collar	1.9	1.7	0.88 (0.83-0.93)	0.88 (0.83-0.93)
Service	6.5	5.9	0.88 (0.85-0.91)	0.88 (0.85-0.91)
Professional	4.7	4.2	0.83 (0.80-0.86)	0.87 (0.84-0.90)
Manager	1.7	1.5	0.79 (0.73-0.85)	0.80 (0.74-0.87)

(Continues)

TABLE 3 (Continued)

Occupational class	Control, %[a]	Case, %[a]	Model 1 OR (95% CI)[b]	Model 2 OR (95% CI)[b]
Others				
Others	20.0	19.9	0.83 (0.81-0.85)	0.87 (0.85-0.89)
After 2003	n = 502 429	n = 105 265		
Blue-collar industry				
Blue-collar	30.9	33.3	1.00	1.00
Service	12.3	12.8	0.99 (0.96-1.01)	0.98 (0.95-1.01)
Professional	4.0	3.9	0.91 (0.87-0.96)	0.92 (0.87-0.97)
Manager	3.6	3.6	1.02 (0.98-1.06)	1.01 (0.97-1.04)
Service industry				
Blue-collar	3.3	3.4	0.95 (0.90-0.99)	0.95 (0.91-1.00)
Service	11.4	11.3	0.96 (0.94-0.99)	0.97 (0.95-1.00)
Professional	1.2	1.1	1.04 (0.94-1.16)	1.06 (0.95-1.17)
Manager	1.9	1.7	1.02 (0.96-1.08)	1.03 (0.97-1.09)
White-collar industry				
Blue-collar	1.9	1.8	0.91 (0.85-0.98)	0.92 (0.86-0.99)
Service	7.2	6.8	0.88 (0.85-0.91)	0.89 (0.86-0.93)
Professional	5.3	4.8	0.88 (0.84-0.93)	0.91 (0.87-0.96)
Manager	1.2	1.0	0.84 (0.79-0.89)	0.85 (0.80-0.90)
Others				
Others	15.7	14.5	0.94 (0.92-0.97)	0.97 (0.95-1.00)

CI, confidence interval; OR, odds ratio.

[a]Data were estimated with five imputed datasets. Percentages may not total 100 because of rounding with multiple imputation.

[b]Conditional logistic regression with multiple imputation, matched for age, admission date, and admitting hospital (model 1); additional adjustment for smoking and alcohol consumption (model 2).

Evidence for socioeconomic gradients for less common cancers remains sparse.[3]

4.3 | Null occupational gradient

The positive socioeconomic gradient for colon cancer has been reported in Western countries.[3,4] The incidence of colorectal cancer has dramatically increased in Japan since the 1970s; the age-standardized incidence rate is now similar to that in the USA.[25] However, we observed a null socioeconomic gradient for male colorectal cancer, as well as for female colorectal cancer in a previous study,[10] which might be partly attributable to potential protective effects of traditional dietary habits in Japan (fish).[26]

4.4 | Positive occupational gradient

For prostate cancer, our observed excess risk with higher occupational class has not been consistently reported worldwide,[3] whereas an excess risk with higher occupational class, possibly related to prostate cancer screening and overdiagnosis, has been reported in USA.[27] In Japan, annual health checkups are conducted in the workplace,[10] which often include an opportunity for prostate cancer screening. Therefore, those in the "other" occupational group (such as the unemployed), who are not actively engaged in paid employment, may not have had a chance for undergoing prostate cancer screening and therefore may have a lower likelihood for over-diagnosis (Table 1); however, empirical evidence for prostate cancer screening in the Japanese population has not been reported yet.[28]

Evidence for socioeconomic gradients for kidney cancer remains sparse.[3] An observed tendency toward a positive socioeconomic gradient for kidney cancer may be partly associated with risk of renal cell carcinoma in higher occupational class men in Japan.[11]

4.5 | Strengths and limitations

As far as we aware, we first found the association of occupational class (as an indicator for SES) and risk of various male cancer incidence in Japan. This study is one of the largest studies for cancer incidence reported in that country. The strengths include accurate diagnosis, which was directly extracted from medical charts in contrast to less accurate diagnosis with claims data,[16] and use of the longest-held

occupation, which is more accurate to measure SES compared with the most recent occupation.[6,7]

However, some limitations should be noted. First, the selection of hospital controls might have introduced selection bias in either direction (toward or away from null). The absence of relevant population-based data did not allow us to obtain population-based controls (as in studies in the Nordic Occupational Cancer Study),[29,30] and one-third of the missing information may reflect selection bias even though we performed multiple imputation. In addition, because the duration of occupation was collected at the questionnaire, recall bias might have introduced. However, occupational profiles of our controls are nationally representative,[10,11] and sensitivity analysis showed the same result. Second, other relevant socioeconomic factors (ie educational attainment and income levels)[21] were not evaluated owing to the limitations of our data. However, a previous large-scale study in Finland showed that male cancer incidence differed across occupational classes even within strata of educational attainment and income levels.[4] Finally, our broad occupational category was not designed to detect occupational exposure and differed from occupational categories to detect specific occupational exposure.[29,30] In addition, we could not assess multiple primary cancer cases or other possible risk factors (overweight, diet, institutional place-based discrimination, physical activity, and cancer screening program).[31-34] Therefore, future studies are warranted to integrate all these aspects of cancer causal pathways.

In conclusion, we have documented socioeconomic inequalities in risk of various male cancer incidence in Japan, which were not explained by smoking and alcohol consumption. The national cancer prevention strategy needs to explicitly incorporate strategies to address occupational class. Since national legislation to restrict indoor smoking has yet to be established in Japan, intensive promotion of preventing passive smoking in (although not limited to) the workplace should be a priority.

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CONFLICT OF INTEREST

None declared.

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SUPPORTING INFORMATION

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

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ORIGINAL RESEARCH

Occupational Class and Risk of Cardiovascular Disease Incidence in Japan: Nationwide, Multicenter, Hospital-Based Case-Control Study

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***Background*—**In contemporary Western settings, higher occupational class is associated with lower risk for cardiovascular disease (CVD) incidence, including coronary heart disease (CHD) and stroke. However, in non-Western settings (including Japan), the occupational class gradient for cardiovascular disease risk has not been characterized.

***Methods and Results*—**Using a nationwide, multicenter hospital inpatient data set (1984–2016) in Japan, we conducted a matched hospital case-control study with ≈1.1 million study subjects. Based on a standard national classification, we coded patients according to their longest-held occupational class (blue-collar, service, professional, manager) within each industrial sector (blue-collar, service, white-collar). Using blue-collar workers in blue-collar industries as the referent group, odds ratios and 95% CIs were estimated by conditional logistic regression with multiple imputation, matched for sex, age, admission date, and admitting hospital. Smoking and drinking were additionally controlled. Higher occupational class (professionals and managers) was associated with excess risk for CHD. Even after controlling for smoking and drinking, the excess odds across all industries remained significantly associated with CHD, being most pronounced among managers employed in service industries (odds ratio, 1.19; 95% CI, 1.08–1.31). On the other hand, the excess CHD risk in higher occupational class was offset by their lower risk for stroke (eg, odds ratio for professionals in blue-collar industries, 0.77; 95% CI, 0.70–0.85).

***Conclusions*—**The occupational "gradient" in cardiovascular disease (with lower risk observed in higher status occupations) may not be a universal phenomenon. In contemporary Japanese society, managers and professionals may experience higher risk for CHD. **(*J Am Heart Assoc*. 2019;8:e011350. DOI: 10.1161/JAHA.118.011350.)**

Key Words: cardiovascular disease • case-control study • cerebrovascular disease • Japan • occupational class • risk factor • socioeconomic gradient

In developed countries, cardiovascular disease (CVD), including coronary heart disease (CHD) and stroke, accounts for a high burden of morbidity and mortality.[1] Although CVD mortality has been declining in the United States as well as in Japan, it accounted for 32% of deaths in 2010 in the United States and is the second leading cause of death in Japan (after cancer).[2,3]

Occupational class is considered to be a fundamental social determinant for CVD risk.[2] In Western settings, including Europe, United States, and Australia, an excess risk of CVD among lower occupational class workers (blue-collar and service workers) is consistently reported.[4–8] The occupational class "gradient" in CVD is in turn attributed to unequal exposures to adverse working conditions (eg, job strain, job insecurity, shift work, sedentarism, secondhand smoke exposure).[7,9–12] Exposure to psychosocial work stress is hypothesized to directly increase CVD risk (eg, through allostatic load and inflammation), as well as indirectly through the patterning of risk behaviors, such as cigarette smoking, excessive drinking, poor sleep, and poor nutrition.[7,8,13,14]

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Clinical Perspective

What Is New?

- In Western countries, the risk of cardiovascular disease is consistently higher in lower status occupations (eg, unskilled workers) compared with higher status occupations (eg, professionals).
- However, in contemporary Japanese society, the pattern of risk was observed to be in the opposite direction, namely, workers in higher status occupations (managerial and professional positions) experienced higher risk for coronary heart disease.
- We found opposite directions of socioeconomic gradients for coronary heart disease and stroke, suggesting that excess risk of coronary heart disease among managers and professionals may be offset by their reduced risk of stroke.

What Are the Clinical Implications?

- The inverse socioeconomic gradient in cardiovascular disease (with lower risk observed in higher status occupations) may not be a universal phenomenon.
- Accordingly, clinicians should adapt their advice to patients based on local realities.
- For example, encouraging the cessation of smoking is a priority for professional/managerial workers in Japan.

However, the "typical" occupational class gradient in CVD that we have come to expect in contemporary Western settings has not been universally observed across time and space.[15] For example, in Japan, while high-quality medical care has been achieved irrespective of socioeconomic status through universal health coverage, annual health check-ups, and community-based comprehensive emergency medical service networks,[16–20] the socioeconomic distribution of major risk behaviors differs markedly from Western countries. Specifically, we have observed that higher-occupational class individuals tend to smoke and drink as much (or sometimes even more) compared with their lower-occupational class counterparts.[21,22] The reason for this pattern is thought to be related to the high levels of job stress among managerial occupations in Japan, stemming from long hours of (unpaid) overtime work as well as the hierarchical corporate structure in Japanese companies and the highly emphasized concept of hospitality to meet customers' expectations.[23] Another potential reason would be the lax social norms on smoking and drinking, eg, as evidenced by the lack of national legislation to restrict indoor smoking.[23]

Accordingly, the goal of the present study was to examine the association between the longest-held occupational class, a proxy for life-long socioeconomic status (SES), and risk for CVD incidence in Japan. Using a nationwide, multicenter inpatient database that includes details of individual-level occupational and clinical information, we sought to describe the occupational class gradient in CHD incidence in Japan.

Methods

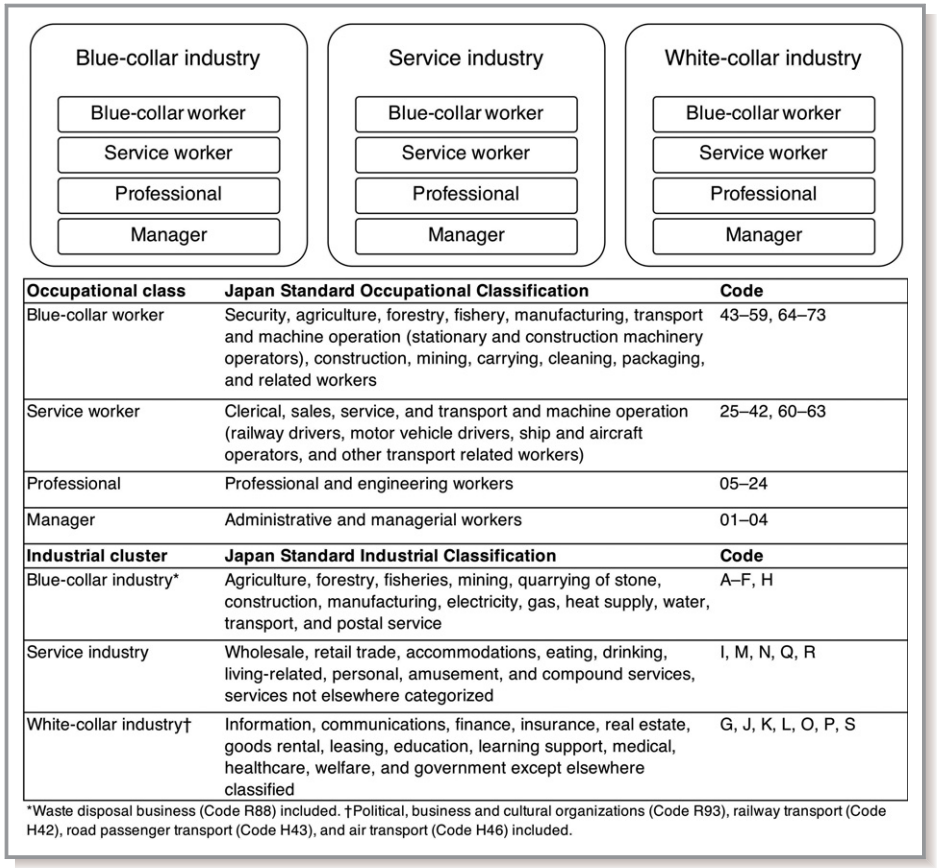
Study Setting

The data that support the findings of this study are available from the Japan Organization of Occupational Health and Safety, but restrictions apply to the availability of these data; they were used under the research agreement for the current study and so are not publicly available. If any person wishes to verify our data, they are most welcome to contact the corresponding author. Using the nationwide clinical and occupational data set (1984–2016) from the Inpatient Clinico-Occupational Database of Rosai Hospital Group (ICOD-R), administered by Japan Organization of Occupational Health and Safety, a multicenter, hospital-based matched case-control study was conducted. Details of ICOD-R and the design of the study have been described elsewhere.[23–27] Briefly, the Rosai Hospital group consists of 33 general hospitals in Japan; it has collected medical chart information confirmed by physicians (including basic sociodemographic characteristics, clinical history and diagnosis of current and

Table 1. The Number of Each Circulatory Disease Sites Among Patients Aged 20 Years and Older in the Nationwide Inpatient Data Set (1984–2016) From the Inpatient Clinico-Occupational Database of Rosai Hospital Group in Japan

Sites	*ICD-9*	*ICD-10*	n (%)
All sites	390–459	I00–99	128 615 (100)
Ischemic heart disease	410–414	I20–25	30 948 (24.1)
Coronary heart disease	413, 410	I20, 21	27 452 (21.3)
Angina pectoris	413	I20	19 781 (15.4)
Acute myocardial infarction	410	I21	7671 (6.0)
Cerebrovascular disease	430–438	I60–69	51 507 (40.0)
Stroke	430–432, 434	I60–63	41 038 (31.9)
Subarachnoid hemorrhage	430	I60	4704 (3.7)
Intracerebral hemorrhage	431	I61	10 245 (8.0)
Cerebral infarction	434	I63	22 242 (17.3)

ICD-9 indicates *International Classification of Diseases, Ninth Revision; ICD-10, International Classification of Diseases, Tenth Revision*.



Occupational class	Japan Standard Occupational Classification	Code
Blue-collar worker	Security, agriculture, forestry, fishery, manufacturing, transport and machine operation (stationary and construction machinery operators), construction, mining, carrying, cleaning, packaging, and related workers	43–59, 64–73
Service worker	Clerical, sales, service, and transport and machine operation (railway drivers, motor vehicle drivers, ship and aircraft operators, and other transport related workers)	25–42, 60–63
Professional	Professional and engineering workers	05–24
Manager	Administrative and managerial workers	01–04
Industrial cluster	**Japan Standard Industrial Classification**	**Code**
Blue-collar industry*	Agriculture, forestry, fisheries, mining, quarrying of stone, construction, manufacturing, electricity, gas, heat supply, water, transport, and postal service	A–F, H
Service industry	Wholesale, retail trade, accommodations, eating, drinking, living-related, personal, amusement, and compound services, services not elsewhere categorized	I, M, N, Q, R
White-collar industry†	Information, communications, finance, insurance, real estate, goods rental, leasing, education, learning support, medical, healthcare, welfare, and government except elsewhere classified	G, J, K, L, O, P, S

*Waste disposal business (Code R88) included. †Political, business and cultural organizations (Code R93), railway transport (Code H42), road passenger transport (Code H43), and air transport (Code H46) included.

Figure 1. Longest-held occupational class, cross-classified with industrial sector.

past diseases, treatment, and outcome for every inpatient) since 1984.[23–27] The clinical diagnosis and comorbid diseases extracted from physicians' medical charts confirmed at discharge are coded according to the *International Classification of Diseases*, *Ninth Revision* (*ICD-9*) or *Tenth Revision* (*ICD-10*).[23–27] The major profile of backgrounds (including sex, age, and occupational class) among patients in the ICOD-R data parallels the Japanese national data.[23,24,27]

From questionnaires completed at the time of admission, the database includes the occupational history of each inpatient (current and 3 most recent jobs, including the age of starting and ending) as well as smoking and alcohol habits.[23–27] The detailed occupational history is coded using the standardized 3-digit codes of the Japan Standard Occupational Classification and Japan Standard Industrial Classification. These correspond, respectively, to the International Standard Industrial Classification and International Standard Occupational Classification; Japan Organization of Occupational Health and Safety updated the previous job codes to be consistent with changes in coding practice according to the revisions of the standardized national classification.[23–27] Written informed consent was obtained before patients completed the questionnaires; trained registrars and nurses are responsible for registering the data. The database currently contains details from >6 million inpatients.

We obtained a deidentified data set under the research agreement between the authors and Japan Organization of Occupational Health and Safety. The research ethics committees of The University of Tokyo, Tokyo (Protocol Number

Table 2. Difference Between Those With Complete Data and Those With Incomplete Data

Characteristics*	n (%) or Mean (SD)		*P* Value
	Incomplete (n=68 181)	Complete (n=1 060 410)	
Case	25 210 (37%)	103 405 (9.8%)	<0.001
Sex, female	4923 (7.2%)	228 412 (22%)	<0.001
Age, y	45 (15)	61 (12)	<0.001
Admission date, financial (y)	1998 (9)	2001 (8)	<0.001

P values for *t* test or Chi-squared test.
*The distribution of admitting hospitals differed between those with complete data and those with incomplete data (*P*<0.001).

Table 3. Background Characteristics Between Cases and Controls

Characteristics*	n (%) or Mean (SD)		*P* Value†
	Control (n=999 976)	Case (n=128 615)	
Female	202 743 (20.3%)	30 592 (23.8%)	<0.001
Age, y	60 (13)	61 (14)	<0.001
Admission date, financial (y)	2001 (8)	2001 (9)	0.13
Occupational class‡	n=957 005	n=103 405	<0.001
Blue-collar industry			
Blue-collar	347 239 (36.3%)	38 824 (37.5%)	
Service	123 213 (12.9%)	12 533 (12.1%)	
Professional	33 755 (3.5%)	2987 (2.9%)	
Manager	38 611 (4.0%)	3960 (3.8%)	
Service industry			
Blue-collar	38 609 (4.0%)	4403 (4.3%)	
Service	156 424 (16.3%)	18 724 (18.1%)	
Professional	8399 (0.9%)	881 (0.9%)	
Manager	19 189 (2.0%)	2055 (2.0%)	
White-collar industry			
Blue-collar	19 711 (2.1%)	1985 (1.9%)	
Service	88 800 (9.3%)	8661 (8.4%)	
Professional	69 905 (7.3%)	7179 (6.9%)	
Manager	13 150 (1.4%)	1213 (1.2%)	
Log-transformed pack-year‡	n=919 976	n=101 458	0.32
	1.90 (1.79)	1.90 (1.79)	
Log-transformed daily ethanol intake‡	n=826 329	n=92 297	<0.001
	2.07 (1.77)	1.95 (1.82)	

*Distribution of admitting hospitals statistically differed between the cases and controls (P<0.001).
†*P*-values were for *t* test and Chi-squared test.
‡Variables contained missing data. Percentage may not total 100 because of rounding.

3890-5) and Kanto Rosai Hospital, Kanagawa (Protocol Number 2014-38) approved the study.

Cases and Controls

The study subjects comprised 1 128 591 patients (128 615 CVD cases and 999 976 controls), aged ≥20 years admitted to the hospital between 1984 and 2016. To select cases and controls from the same population, we randomly sampled 10 controls for each case, matched by sex (men/women), age (in the same 5-year age category), admission date (in the same financial year), and admitting hospital (in the same admitting hospital).[24,26,27] The matching process, however, generated fewer than 10 controls for some cases (the average number of controls for each case, 8 [range 1–10]; the percentage of cases matched to 10 controls, 54.9%). The mean age [mean (SD)] for the original population and the matched population was, respectively, 55 (19) years and 60 (13) years. Controls who were later hospitalized for CVD were not eligible to be cases.

The cases were those patients whose main diagnosis was initial CVD (*ICD-9*, 390–459 and *ICD-10*, I00–99), confirmed by physicians at discharge along with clinical examinations or treatments, including ECGs, computerized tomography scans, catheter angiography/intervention, and surgery. We defined CVD incidence as the first ever hospital admission among patients who did not have a previous history of any CVDs. Validation for the diagnosis corresponding to *ICD-9* or *ICD-10* in the database has been described elsewhere.[23–27] The database is unique to the Rosai Hospital group, therefore it differs from medical claims data, which may be less accurate for diagnosis.[28] We specified CHD, which comprised with angina pectoris (*ICD-9*, 413 and *ICD-10*, I20) and acute myocardial infarction (*ICD-9*, 410 and *ICD-10*, I21, Table 1). We also specified stroke, which comprised with subarachnoid hemorrhage, intracerebral hemorrhage, and cerebral infarction (Table 1).

Based on the methodology used in previous studies, our controls comprised patients admitted to the hospitals with the following diagnoses, which were not related to occupational class in ICOD-R[23,24,27]: eye and ear disease (*ICD-9*, 360–389 and *ICD-10*, H00–H95; 31.1%), genitourinary disease (*ICD-9*, 580–629 and *ICD-10*, N00–N99; 31.1%), infection (*ICD-9*, 1–136 and *ICD-10*, A00–B99; 10.7%), skin diseases (*ICD-9*, 680-709 and *ICD-10*, L00-L99; 5.9%), symptoms and ill-health conditions (*ICD-9*, 780-799 and *ICD-10*, R00-R99; 7.3%), or other diseases such as congenital malformations (*ICD-9*, 280-289, 740-779, and *ICD-10*, D50-D77, P00-P96, Q00-Q99; 13.9%). We excluded controls (1) who had a history of CVD or (2) who were not admitted to the hospitals for the first time.

Longest-Held Occupational Class Cross-Classified by Industry Sector

To classify occupational class from the comprehensive list of occupations (current and up to 3 most recent jobs) listed in ICOD-R, we grouped the longest-held occupation for each patient into 1 of 4 occupational classes: blue-collar, service, professional, and manager. Each patient was also cross-classified into 1 of 3 industrial sectors: blue-collar, service, and white-collar, based on the approach adopted in previous studies (Figure 1).[23,24,27] Those who were not actively engaged in paid employment, such as homemakers, students, and unemployed workers, were excluded. The average length of the longest held jobs was 27 years in ICOD-R, and the length was not significantly associated with risk for CVD in a

Table 4. Odds Ratios of Each Occupational Class Associated With Risk for Coronary Heart Disease, Stroke, and Overall CVD Incidence

Characteristics	Control %*	Case, %*	Odds Ratio (95% CI)			
			Model 1†	*P* Value	Model 2‡	*P* Value
Coronary heart disease	n=226 378	n=27 452				
Occupational class						
Blue-collar industry						
Blue-collar	34.6	33.6	1.00		1.00	
Service	13.9	13.8	1.09 (1.04–1.13)	<0.001	1.08 (1.04–1.13)	<0.001
Professional	4.1	3.8	1.05 (0.97–1.13)	0.22	1.07 (0.99–1.16)	0.08
Manager	4.5	4.9	1.19 (1.11–1.27)	<0.001	1.19 (1.11–1.27)	<0.001
Service industry						
Blue-collar	4.1	3.9	1.01 (0.94–1.09)	0.83	1.01 (0.93–1.08)	0.86
Service	15.8	16.8	1.10 (1.06–1.15)	<0.001	1.10 (1.06–1.15)	<0.001
Professional	0.9	0.9	1.13 (0.97–1.32)	0.11	1.16 (0.99–1.35)	0.06
Manager	2.2	2.4	1.20 (1.09–1.31)	<0.001	1.19 (1.08–1.31)	<0.001
White-collar industry						
Blue-collar	2.1	2.1	1.07 (0.98–1.18)	0.15	1.08 (0.99–1.19)	0.09
Service	9.4	9.2	1.04 (0.99–1.09)	0.17	1.05 (1.00–1.11)	0.05
Professional	7.0	7.0	1.05 (0.99–1.11)	0.08	1.10 (1.04–1.17)	<0.001
Manager	1.5	1.5	1.06 (0.94–1.19)	0.35	1.06 (0.95–1.19)	0.29
Log-transformed pack-year, mean	2.1	2.3			1.15 (1.14–1.16)	<0.001
Log-transformed daily ethanol intake, mean	2.3	2.2			0.95 (0.94–0.96)	<0.001
Angina pectoris	n=163 736	n=19 781				
Occupational class						
Blue-collar industry						
Blue-collar	34.1	32.8	1.00		1.00	
Service	13.9	14.1	1.12 (1.06–1.18)	<0.001	1.11 (1.05–1.17)	<0.001
Professional	4.1	4.0	1.10 (1.00–1.21)	0.04	1.11 (1.02–1.22)	0.02
Manager	4.4	4.9	1.24 (1.14–1.34)	<0.001	1.23 (1.14–1.33)	<0.001
Service industry						
Blue-collar	4.1	3.7	0.92 (0.84–1.01)	0.08	0.92 (0.84–1.01)	0.07
Service	16.2	16.9	1.08 (1.03–1.14)	<0.001	1.08 (1.03–1.13)	0.001
Professional	0.9	0.9	1.13 (0.90–1.42)	0.27	1.15 (0.92–1.45)	0.20
Manager	2.2	2.4	1.21 (1.08–1.35)	0.001	1.19 (1.07–1.34)	0.002
White-collar industry						
Blue-collar	2.1	2.1	1.11 (0.99–1.24)	0.07	1.12 (1.00–1.25)	0.05
Service	9.4	9.3	1.05 (0.99–1.11)	0.11	1.06 (1.00–1.12)	0.05
Professional	7.1	7.4	1.08 (1.01–1.15)	0.02	1.12 (1.05–1.19)	<0.001
Manager	1.5	1.5	1.12 (0.98–1.28)	0.09	1.12 (0.98–1.28)	0.08
Log-transformed pack-year, mean	2.0	2.2			1.11 (1.10–1.12)	<0.001
Log-transformed daily ethanol intake, mean	2.2	2.2			0.98 (0.97–0.99)	<0.001
Acute myocardial infarction	n=62 642	n=7671				

Continued

Table 4. Continued

Characteristics	Control %*	Case, %*	Odds Ratio (95% CI)			
			Model 1†	*P* Value	Model 2‡	*P* Value
Occupational class						
Blue-collar industry						
Blue-collar	35.8	35.6	1.00		1.00	
Service	13.9	13.0	1.01 (0.93–1.11)	0.79	1.01 (0.92–1.10)	0.85
Professional	4.1	3.5	0.92 (0.80–1.06)	0.26	0.97 (0.85–1.12)	0.70
Manager	4.7	4.8	1.07 (0.95–1.21)	0.28	1.07 (0.95–1.22)	0.26
Service industry						
Blue-collar	3.9	4.7	1.25 (1.09–1.42)	0.002	1.25 (1.09–1.43)	0.001
Service	14.6	16.3	1.16 (1.07–1.26)	<0.001	1.16 (1.07–1.26)	<0.001
Professional	0.9	0.9	1.12 (0.82–1.52)	0.47	1.17 (0.86–1.59)	0.32
Manager	2.2	2.5	1.18 (1.00–1.38)	0.05	1.18 (1.00–1.39)	0.05
White-collar industry						
Blue-collar	2.3	2.2	0.98 (0.78–1.24)	0.89	1.00 (0.78–1.28)	>0.99
Service	9.4	8.9	1.01 (0.91–1.11)	0.91	1.03 (0.93–1.14)	0.53
Professional	6.6	6.2	0.98 (0.85–1.12)	0.73	1.06 (0.92–1.23)	0.37
Manager	1.5	1.3	0.90 (0.67–1.21)	0.46	0.92 (0.68–1.24)	0.57
Log-transformed pack-year, mean	2.2	2.6			1.25 (1.22–1.27)	<0.001
Log-transformed daily ethanol intake, mean	2.4	2.1			0.88 (0.86–0.89)	<0.001
Stroke	n=312 675	n=41 038				
Occupational class						
Blue-collar industry						
Blue-collar	40.1	43.0	1.00		1.00	
Service	12.1	11.3	0.94 (0.90–0.98)	0.004	0.93 (0.89–0.97)	0.001
Professional	3.2	2.4	0.77 (0.70–0.85)	<0.001	0.77 (0.70–0.85)	<0.001
Manager	4.0	3.6	0.91 (0.85–0.97)	0.005	0.88 (0.83–0.95)	<0.001
Service industry						
Blue-collar	4.0	4.5	1.08 (1.02–1.15)	0.01	1.08 (1.02–1.15)	0.01
Service	15.1	16.2	1.02 (0.98–1.06)	0.30	1.01 (0.98–1.05)	0.47
Professional	0.9	0.9	0.97 (0.85–1.10)	0.59	0.99 (0.87–1.13)	0.89
Manager	2.0	2.0	0.98 (0.90–1.06)	0.60	0.96 (0.89–1.04)	0.36
White-collar industry						
Blue-collar	2.1	1.9	0.88 (0.81–0.95)	0.002	0.87 (0.80–0.95)	0.001
Service	8.6	7.2	0.81 (0.77–0.85)	<0.001	0.81 (0.78–0.86)	<0.001
Professional	6.7	6.0	0.85 (0.81–0.89)	<0.001	0.87 (0.83–0.91)	<0.001
Manager	1.3	1.1	0.84 (0.74–0.96)	0.01	0.84 (0.73–0.95)	0.01
Log-transformed pack-year, mean	1.9	2.1			1.08 (1.07–1.09)	<0.001
Log-transformed daily ethanol intake, mean	2.1	2.2			1.07 (1.06–1.08)	<0.001
Overall	n=999 976	n=128 615				
Occupational class						
Blue-collar industry						
Blue-collar	35.8	37.2	1.00		1.00	

Continued

Table 4. Continued

Characteristics	Control %*	Case, %*	Odds Ratio (95% CI)			
			Model 1†	*P* Value	Model 2‡	*P* Value
Service	13.0	12.4	0.99 (0.96–1.01)	0.18	0.98 (0.96–1.00)	0.05
Professional	3.7	3.1	0.89 (0.85–0.93)	<0.001	0.90 (0.86–0.93)	<0.001
Manager	4.0	3.9	1.01 (0.98–1.05)	0.46	1.00 (0.96–1.03)	0.84
Service industry						
Blue-collar	4.0	4.3	1.04 (1.00–1.08)	0.05	1.04 (1.00–1.08)	0.05
Service	16.4	17.7	1.06 (1.03–1.08)	<0.001	1.05 (1.03–1.07)	<0.001
Professional	0.9	0.9	1.01 (0.94–1.09)	0.74	1.03 (0.96–1.10)	0.43
Manager	2.0	2.0	1.03 (0.98–1.08)	0.31	1.01 (0.96–1.06)	0.60
White-collar industry						
Blue-collar	2.1	2.0	0.97 (0.93–1.02)	0.25	0.97 (0.93–1.02)	0.24
Service	9.4	8.4	0.90 (0.88–0.92)	<0.001	0.91 (0.88–0.93)	<0.001
Professional	7.4	6.9	0.91 (0.89–0.94)	<0.001	0.94 (0.92–0.97)	<0.001
Manager	1.4	1.2	0.91 (0.85–0.98)	0.01	0.91 (0.85–0.98)	0.01
Log-transformed pack-year, mean	1.9	2.1			1.09 (1.08–1.09)	<0.001
Log-transformed daily ethanol intake, mean	2.2	2.2			1.02 (1.02–1.03)	<0.001

*Estimated with 5 imputed data. Percentage may not total 100 because of multiple imputation and rounding. The characteristics of all variables statistically differed between the case and controls ($P<0.05$ for *t* test or Chi-squared test in an imputed data set).
†Conditional logistic regression with multiple imputation, matched for sex, age, admission date, and admitting hospital.
‡Additional adjustment for smoking and alcohol consumption.

prior analysis (data not shown). We mainly focused on the longest-held jobs, which meant less possibility of misclassification of occupational class compared with the current/most recent jobs.[23,24,27]

Covariates

Confounding factors included sex, age, admission date, and admitting hospital, controlled by exact matching

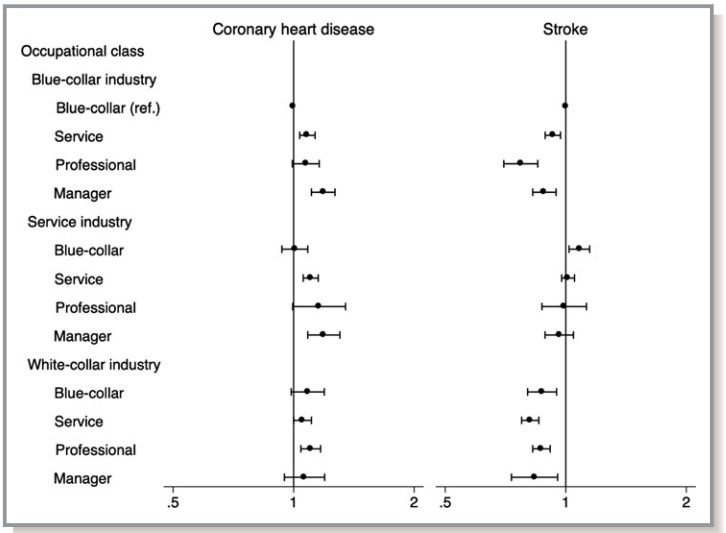


Figure 2. Risk for coronary heart disease and stroke incidence associated with occupational class. The odds ratio (dot) and 95% CI (bar) were estimated by conditional logistic regression with multiple imputation, matched for age, admission date, and admitting hospital, additionally adjusted for smoking and alcohol consumption. The numbers of cases and controls used for analysis were, respectively, 27 452 and 226 378 for coronary heart disease and 41 038 and 312 675 for stroke.

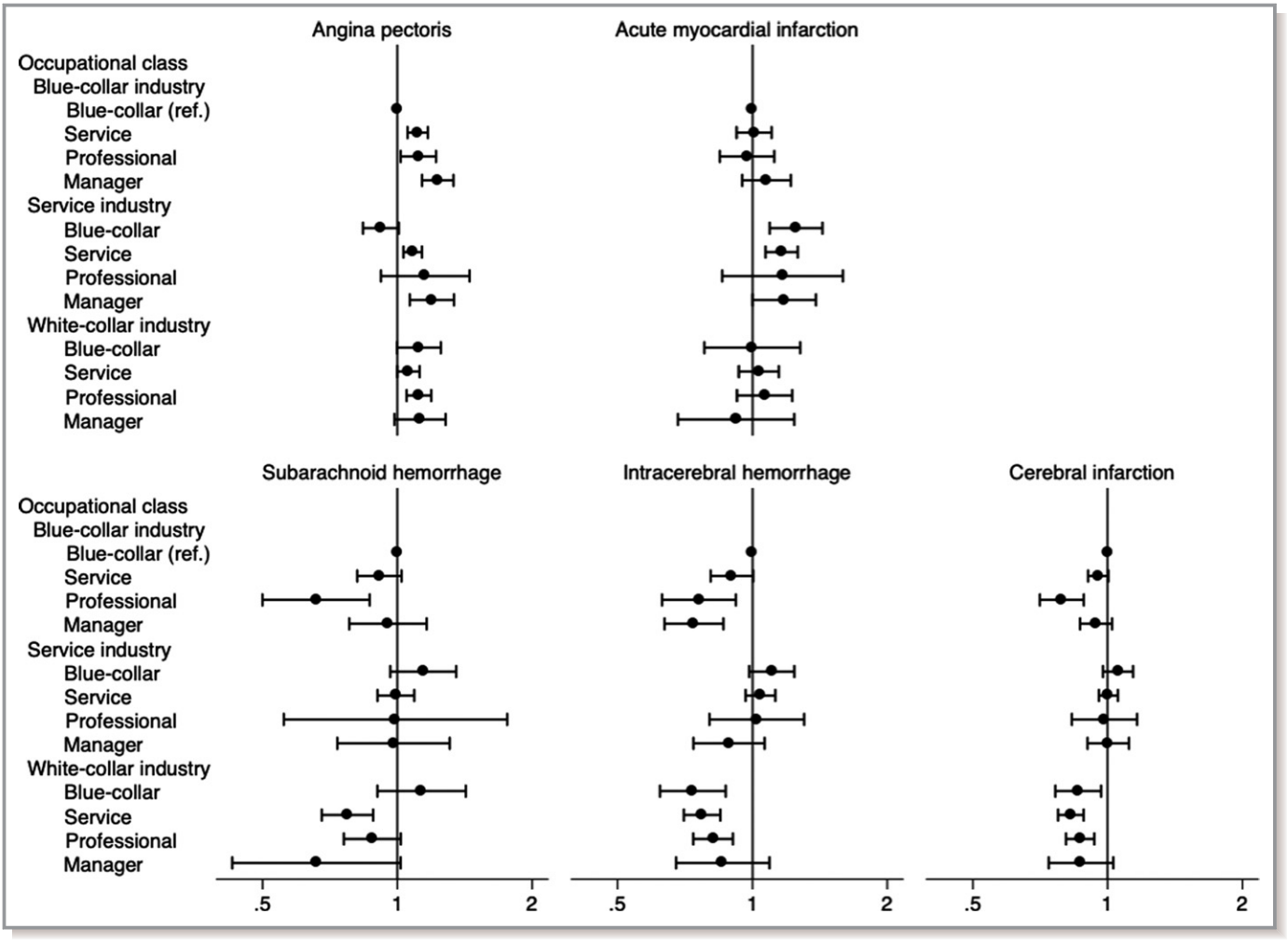


Figure 3. Odds ratios associated with occupational class for incidence of angina pectoris, acute myocardial infarction, subarachnoid hemorrhage, intracerebral hemorrhage, and cerebral infarction. The odds ratio (dot) and 95% CI (bar) were estimated by conditional logistic regression with multiple imputation, matched for age, admission date, and admitting hospital, additionally adjusted for smoking and alcohol consumption. The numbers of cases and controls used for analysis were, respectively, 19 781 and 163 736 for angina pectoris, 7671 and 62 642 for acute myocardial infarction, 4704 and 36 535 for subarachnoid hemorrhage, 10 245 and 79 321 for intracerebral hemorrhage, and 22 242 and 168 286 for cerebral infarction.

procedure.[23–27] To control for potential changes in diagnosis and treatment as well as regional variations in lifestyle behaviors (such as salt intake) over time, we created dummies for admission date and admitting hospital. Smoking (log-transformed pack-years) and alcohol consumption (log-transformed ethanol gram per day) were included in the regression models as potential mediating variables.[23–27]

Statistical Analysis

We conducted multiple imputation for missing data among the 1 128 591 study subjects, using all variables in the present study with Multiple Imputation by Chained Equations method;[29] and 5 imputed data sets were generated.[23,24,27,30] Overall 20% of respondents had missing data, and we performed multiple imputation for the following missing data because of the background differences between those with complete and incomplete data (Table 2): occupational class (n=68 181, 6.0%), smoking (n=107 157, 9.5%), and alcohol consumption (n=209 965, 18.6%).

Odds ratios (ORs) and 95% CIs of CHD, stroke, and overall CVD incidence were estimated by conditional logistic regression with multiple imputation. Blue-collar workers in blue-collar industries served as the referent group for all analyses. Cases were matched to controls based on sex, age, admission date, and admitting hospital (model 1).[23,24,27,30] Smoking and alcohol consumption were additionally adjusted in model 2.[23,24,27,30] In addition, ORs and 95% CIs for specific types of CHD and stroke (angina pectoris, AMI, subarachnoid

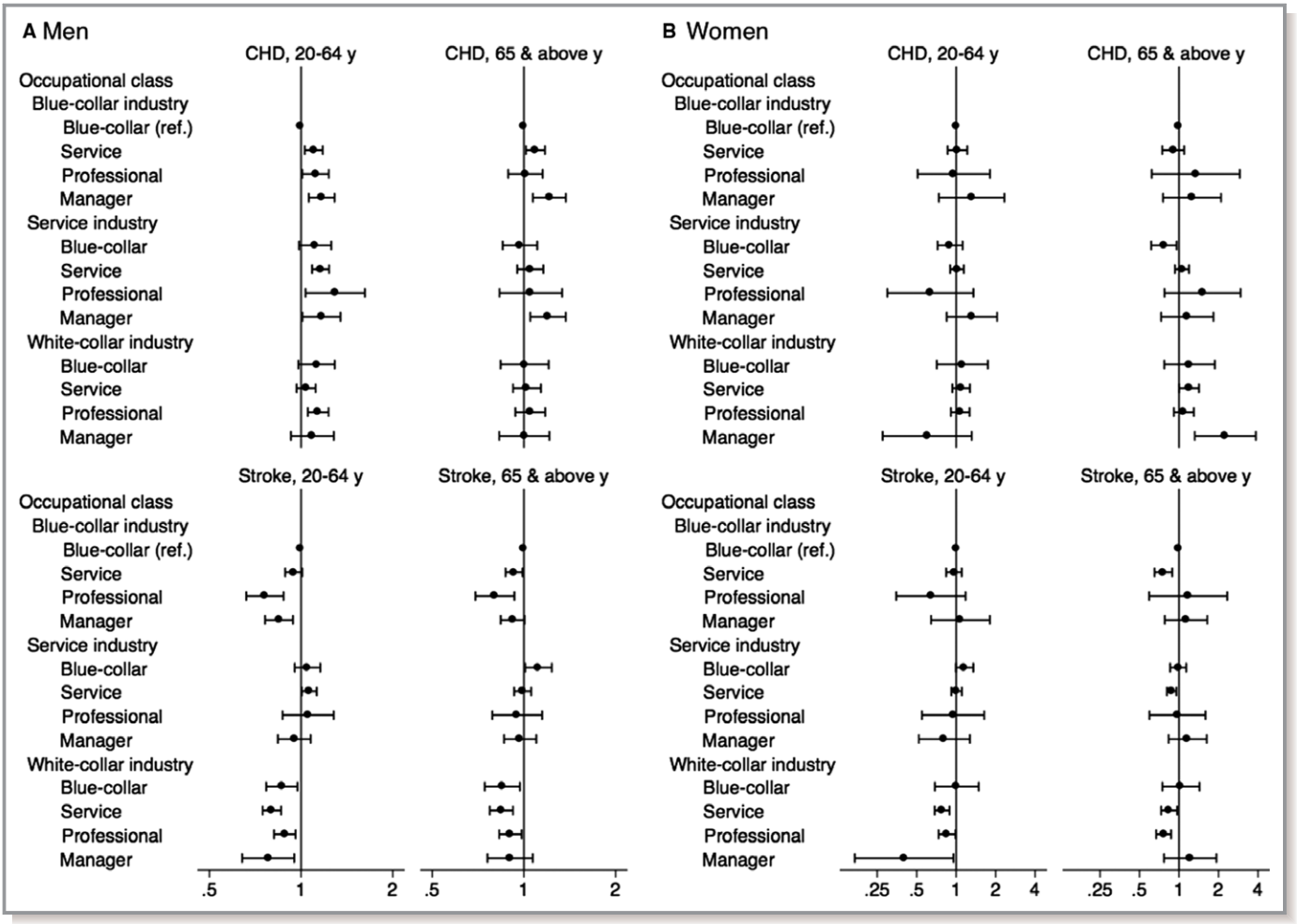


Figure 4. Occupational class gradients stratified by sex and age. The odds ratio (dot) and 95% CI (bar) were estimated by conditional logistic regression with multiple imputation, matched for age, admission date, and admitting hospital, additionally adjusted for smoking and alcohol consumption. The numbers of cases and controls used for analysis were, respectively, (**A**) for men, 13 797 and 118 423 for CHD in 20 to 64 years, 8897 and 74 520 for CHD in ≥65 years, 17 240 and 143 109 for stroke in 20 to 64 years, 14 609 and 110 515 for stroke in ≥65 years; (**B**) for women, 2546 and 18 472 for CHD in 20 to 64 years, 2212 and 14 963 for CHD in ≥65 years, 4170 and 29 298 for stroke in 20 to 64 years, 5019 and 29 753 for stroke in ≥65 years. CHD indicates coronary heart disease.

hemorrhage, intracerebral hemorrhage, and cerebral infarction) were estimated separately.

In sensitivity analyses, we performed stratified analysis with sex (men versus women) and age (20–64 versus ≥65 years).[31] Additionally, to explore potential heterogeneity introduced by secular changes in diagnostic practices or treatment, we performed stratified analysis according to admission period (1984–2002 versus 2003–2016).[25,27] To check for potential selection bias in hospital controls, alternative control groups (all benign diseases) were applied. To check for potential bias on the matching process, a lower matching ratio (4 controls per each case) was applied. We also assessed the association between the most recent jobs and risk of CVD, assigning the most recent occupational class as the occupational exposure.

Alpha was set at 0.05, and all *P* values were 2-sided. Data were analyzed using STATA/MP13.1 (StataCorp LP, College Station, TX).

Results

The background distribution of the cases and controls are shown in Table 3. Most of the distributions differed between the cases and controls, including occupational class.

Compared with blue-collar workers in blue-collar industries, higher occupational class (professionals and managers) was associated with an excess risk for CHD (Table 4). Even after controlling for smoking and alcohol consumption, the elevated odds remained statistically significant across all industries, being most pronounced in service industries (OR in

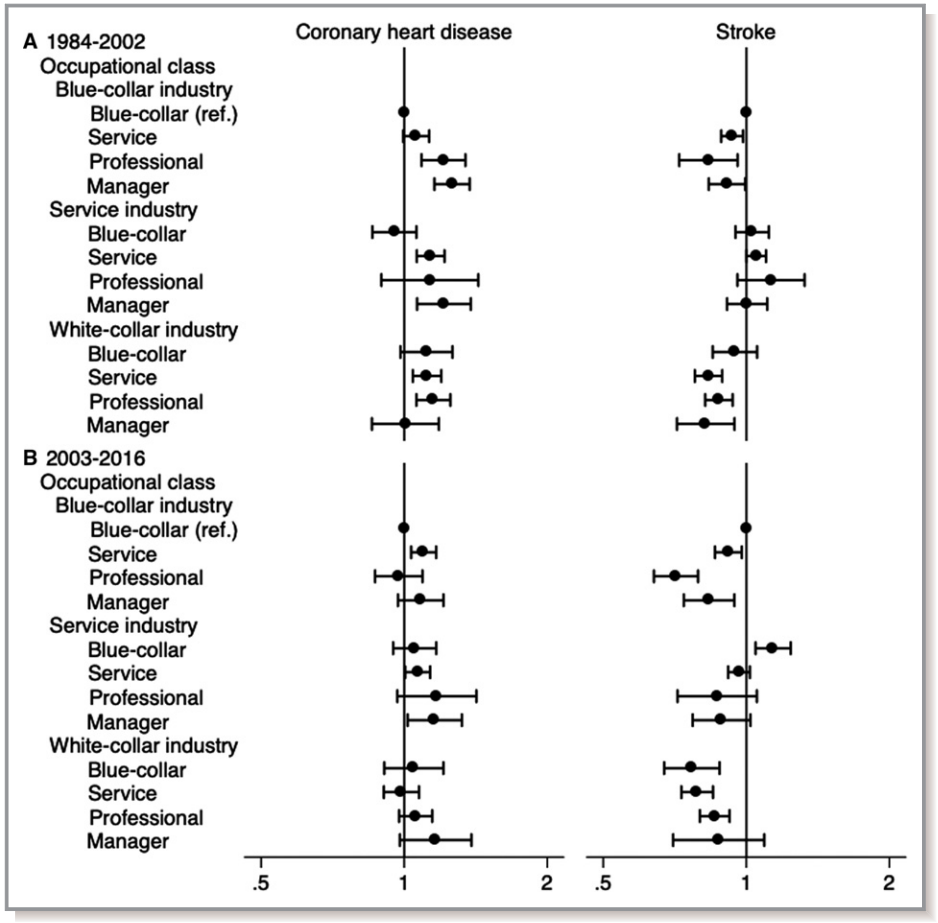


Figure 5. Occupational class gradients stratified by admission period. The odds ratio (dot) and 95% CI (bar) were estimated by conditional logistic regression with multiple imputation, matched for age, admission date, and admitting hospital, additionally adjusted for smoking and alcohol consumption. The numbers of cases and controls used for analysis were, respectively, (**A**) for 1984–2002, 14 170 and 117 229 for coronary heart disease and 24 205 and 184 525 for stroke; (**B**) for 2003–2016, 13 282 and 109 149 for coronary heart disease and 16 833 and 128 150 for stroke.

managers, 1.19; 95% CI 1.08—1.31; model 2, Figure 2 and Table 4). In the strata of high-occupational classes (managers and professionals) in blue- and white-collar industries, the odds for angina pectoris were elevated, while the odds for acute myocardial infarction were shifted toward the null association (Figure 3 and Table 4). However, in service industries, the odds in that high-occupational status remained elevated for both angina pectoris and myocardial infarction. (Figure 3 and Table 4).

By contrast, compared with blue-collar workers in blue-collar industries, higher occupational class was associated with a reduced risk for stroke incidence (Table 4). The protective associations ranged from 0.77 for professionals working in blue-collar industries to 0.88 for managers working in blue-collar industries (model 2, Figure 2 and Table 4). These patterns were repeated for specific subtypes of stroke: subarachnoid hemorrhage, intracerebral hemorrhage, and cerebral infarction (Figure 3).

As a whole, higher occupational class was weakly associated with reduced risk for overall CVD incidence (Table 4), suggesting that the excess risk of CHD among managers/professionals was offset by reduced risk for stroke. In sensitivity analyses, the results stratified by sex and age (Figure 4) and admission period (Figure 5), as well as the results estimated with alternative hospital controls (Figure 6), showed almost the same socioeconomic patterns. The odds ratios estimated with a lower matching ratio (4 controls per case, Table 5), as well as the odds ratios estimated with the most recent occupational class (Figure 7 and Table 6), also showed the same socioeconomic pattern.

Discussion

The direction of association between occupational class and CHD incidence in Japan appears to be opposite to the pattern observed in contemporary Western countries.[2,4–7] In addition,

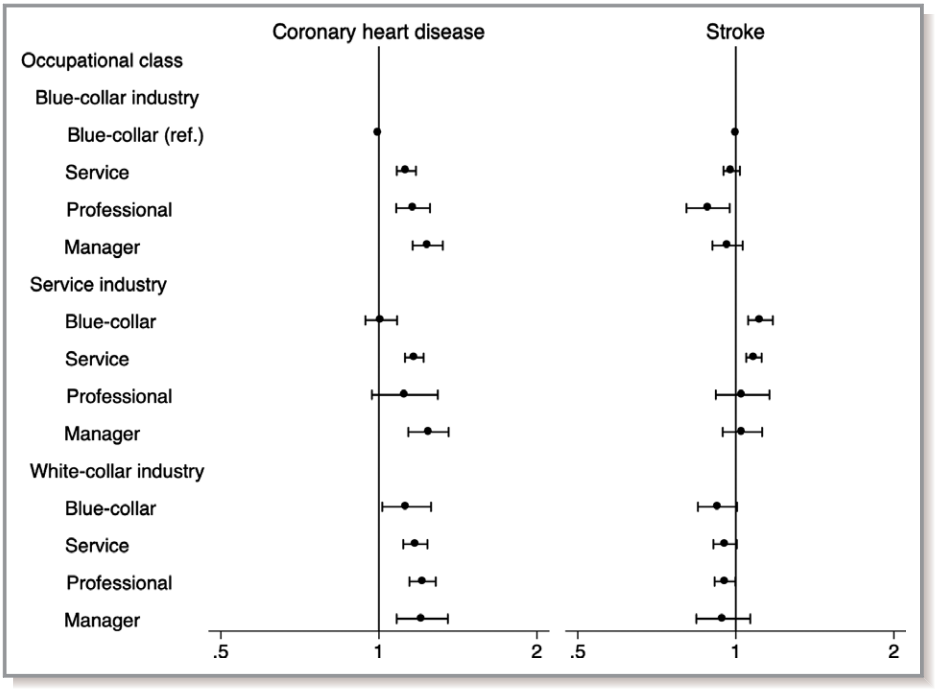


Figure 6. Odds ratio in each occupational class for coronary heart disease and stroke incidence estimated with alternative control groups. The odds ratio (dot) and 95% CI (bar) were estimated by conditional logistic regression with multiple imputation, matched for age, admission date, and admitting hospital, additionally adjusted for smoking and alcohol consumption. The control group comprised patients diagnosed with benign neoplasm (10.0%), digestive disease (14.4%), endocrine disease (3.5%), eye and ear disease (9.9%), genitourinary system disease (8.3%), infectious disease (2.7%), injury (15.8%), mental disease (0.7%), musculoskeletal disease (15.6%), nerve system disease (3.7%), respiratory disease (6.8%), skin diseases (1.4%), symptoms and ill-health conditions (2.1%), or other diseases such as congenital malformations (3.6%). The numbers of cases and controls used for analysis were, respectively, 22 553 and 220 909 for coronary heart disease and 32 021 and 306 689 for stroke.

we have demonstrated for the first time the opposite directions of socioeconomic gradients for 2 major CVDs, ie, CHD and stroke, within the same country, which suggests excess risk of CHD may be offset by reduced risk of stroke. Furthermore, smoking and alcohol consumption did not fully explain the observed socioeconomic inequalities in Japan, where national strategies that include high-quality cardiovascular prevention and treatment has been provided irrespective of socioeconomic status.[16]

As concluded in a recent systematic review of studies in Western countries,[7] cardiovascular risk factors are strongly patterned by SES, including occupational class, such that socioeconomically advantaged groups enjoy lower CVD risk. However, this socioeconomic "gradient" is not an immutable phenomenon over history. Indeed during the first half of the twentieth century, when chronic disease incidence and mortality was on the rise, CHD was identified as a disease of affluence (as depicted in terms such as "the executive coronary"),[15] and early descriptions of CHD among higher occupational classes date as far back as Osler in 1910.[32] Over the course of the twentieth century, the socioeconomic gradient in CHD reversed, reflecting advances in our understanding of the risk factors for CHD (such as smoking, regular exercise, diet, as well as treatment for high blood pressure and dyslipidemia), and the more rapid adoption of these behaviors by the socioeconomically advantaged classes.[15]

Our finding of a reverse gradient by occupational class for coronary disease in Japan may buck this trend. Part of the reason for the observed pattern may be because of the persistently high rates of smoking (by Western standards) even among professionals/managers in Japan, as well as the high rates of heavy drinking in Japanese corporate culture.[21,22] Nevertheless, our results could not be completely explained by controlling for smoking and drinking habits, suggesting that other cardiovascular risk factors, such as insufficient physical activity, hypertension, diabetes mellitus, and obesity, may play a role.[7,13] For example, the lowest levels of physical activity and higher prevalence of hypertension were reported among higher occupational class in Japan.[33,34]

Table 5. Odds Ratios of Each Occupational Class Associated With Risk for Coronary Heart Disease and Stroke Estimated With 4 Matched Controls Per Each Case

Occupational Class	Odds Ratio (95% CI)*			
	Coronary Heart Disease		Stroke	
	Model 1†	Model 2‡	Model 1†	Model 2‡
Blue-collar industry				
Blue-collar	1.00	1.00	1.00	1.00
Service	1.08 (1.04–1.14)	1.08 (1.03–1.13)	0.94 (0.89–0.98)	0.93 (0.89–0.97)
Professional	1.06 (0.98–1.14)	1.08 (1.00–1.17)	0.77 (0.70–0.85)	0.77 (0.70–0.85)
Manager	1.19 (1.11–1.28)	1.19 (1.11–1.28)	0.91 (0.85–0.98)	0.89 (0.83–0.95)
Service industry				
Blue-collar	1.01 (0.93–1.09)	1.01 (0.93–1.09)	1.07 (1.01–1.14)	1.07 (1.01–1.14)
Service	1.10 (1.05–1.15)	1.10 (1.05–1.15)	1.03 (0.99–1.07)	1.02 (0.98–1.06)
Professional	1.08 (0.92–1.27)	1.11 (0.94–1.30)	0.94 (0.83–1.08)	0.96 (0.84–1.10)
Manager	1.21 (1.10–1.34)	1.21 (1.10–1.33)	1.01 (0.93–1.10)	0.99 (0.91–1.08)
White-collar industry				
Blue-collar	1.03 (0.93–1.14)	1.05 (0.95–1.16)	0.88 (0.81–0.96)	0.87 (0.80–0.95)
Service	1.03 (0.98–1.09)	1.05 (1.00–1.11)	0.82 (0.78–0.86)	0.82 (0.78–0.86)
Professional	1.04 (0.98–1.11)	1.09 (1.03–1.16)	0.84 (0.80–0.88)	0.86 (0.82–0.91)
Manager	1.06 (0.93–1.20)	1.07 (0.95–1.22)	0.84 (0.74–0.97)	0.84 (0.73–0.96)

*Estimated with 5 imputed data. The numbers of cases and controls used for analysis were, respectively, 27 452 and 104 391 for coronary heart disease and 41 038 and 152 037 for stroke.
†Conditional logistic regression with multiple imputation, matched for sex, age, admission date, and admitting hospital.
‡Additional adjustment for smoking and alcohol consumption.

Among neighboring East-Asian countries, eg, South Korea, metabolic syndrome has also been reported to be more prevalent in higher occupational classes.[35] In addition, emerging workplace-related concerns of long working hours and job stress for cardiovascular risk may also play a role.[9,36,37] Higher occupational class individuals, particularly in service industries in Japan, are likely vulnerable to stress stemming from striving to meet customer expectations, which sometimes has led to well-publicized instances of death from overwork ("karoshi").[23]

Although CHD and stroke are considered to share major conventional risk factors such as smoking,[7,8,13,14] notably, the pattern of occupational class gradients for CHD and stroke were in the opposite direction, ie, lower stroke risk among managers/professionals. The opposing patterns of the occupational gradient for CHD and stroke suggest that the 2 diseases have different origins, despite sharing several major risk factors (such as smoking and hypertension). For example, early life course socioeconomic status may also partly play a role in the reduced risk of stroke incidence among higher occupational classes via chronic *Helicobacter pylori* infection.[13,38,39] The prevalence of *H. pylori* infection is high in the general population in Japan (≈70%),[40,41] yet studies have linked earlier acquisition with more disadvantaged childhood socioeconomic circumstances (related to sanitation, overcrowding, rural residence).[13,38,39] Chronic *H. pylori* infection has been linked with chronic vascular inflammation, which increases the risk for stroke incidence.[39]

Some limitations should be noted in the present study. First, selection of hospital controls is potentially subject to bias (either toward or away from the null association). However, our sensitivity analysis using alternative control groups (all benign diseases) yielded almost identical results. Additionally, the distribution of occupational classes in the ICOD-R data parallels the Japanese national data.[23,24,27] Although hospital case-control studies are not representative of the national population (thereby limiting external generalizability), internal validity is maintained by sampling the controls from the same source population that sought treatment in the selected hospitals. Our matching procedure was not able to generate 10 controls for every case, which resulted in residual statistical differences in the baseline characteristics between the cases and controls. Although relatively minor, these differences may have nonetheless resulted in some residual confounding. Second, other relevant socioeconomic factors, ie, educational attainment and income

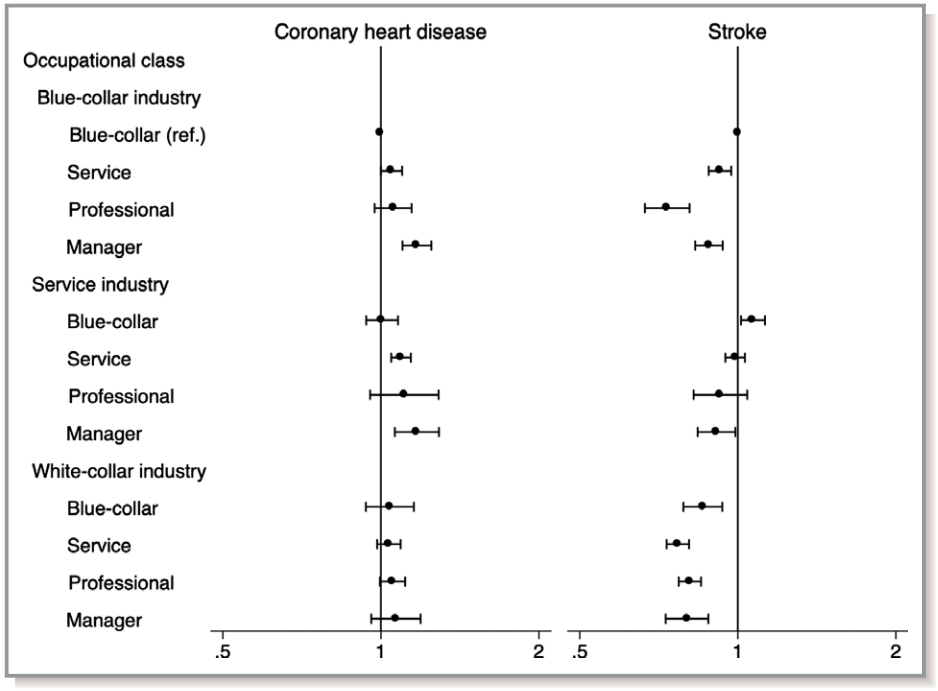


Figure 7. Risks of coronary heart disease and stroke incidence associated with most recent occupational class. The odds ratio (dot) and 95% CI (bar) were estimated by conditional logistic regression with multiple imputation, matched for age, admission date, and admitting hospital, additionally adjusted for smoking and alcohol consumption. The numbers of cases and controls used for analysis were, respectively, 27 306 and 225 227 for coronary heart disease and 40 793 and 310 901 for stroke.

Table 6. Odds Ratios of Most Recent Occupational Class Associated With Risk for Coronary Heart Disease and Stroke

	Odds Ratio (95% CI)*			
	Coronary Heart Disease		Stroke	
Occupational Class	Model 1†	Model 2‡	Model 1†	Model 2‡
Blue-collar industry				
Blue-collar	1.00	1.00	1.00	1.00
Service	1.05 (1.01–1.10)	1.05 (1.00–1.10)	0.93 (0.89–0.98)	0.92 (0.88–0.97)
Professional	1.03 (0.95–1.12)	1.05 (0.97–1.14)	0.73 (0.67–0.81)	0.73 (0.67–0.81)
Manager	1.17 (1.10–1.24)	1.17 (1.10–1.25)	0.90 (0.85–0.96)	0.88 (0.83–0.94)
Service industry				
Blue-collar	1.01 (0.94–1.08)	1.01 (0.94–1.08)	1.07 (1.02–1.13)	1.07 (1.01–1.13)
Service	1.10 (1.05–1.14)	1.09 (1.05–1.14)	0.99 (0.95–1.04)	0.99 (0.95–1.03)
Professional	1.07 (0.92–1.25)	1.11 (0.95–1.29)	0.90 (0.80–1.02)	0.93 (0.82–1.04)
Manager	1.18 (1.07–1.30)	1.17 (1.06–1.29)	0.93 (0.86–1.01)	0.91 (0.84–0.99)
White-collar industry				
Blue-collar	1.02 (0.92–1.14)	1.04 (0.94–1.16)	0.86 (0.79–0.93)	0.86 (0.79–0.93)
Service	1.02 (0.97–1.08)	1.04 (0.98–1.09)	0.77 (0.73–0.81)	0.77 (0.73–0.81)
Professional	1.01 (0.95–1.06)	1.05 (1.00–1.11)	0.79 (0.75–0.83)	0.81 (0.77–0.85)
Manager	1.05 (0.94–1.17)	1.07 (0.96–1.19)	0.80 (0.73–0.88)	0.80 (0.73–0.88)

*Estimated with 5 imputed data. The numbers of cases and controls used for analysis were, respectively, 27 306 and 225 227 for coronary heart disease and 40 793 and 310 901 for stroke.
†Conditional logistic regression with multiple imputation, matched for sex, age, admission date, and admitting hospital.
‡Additional adjustment for smoking and alcohol consumption.

levels,[2] were not assessed because of the limitations of our data set. However, in previous studies based in Japan, cardiovascular risk was not strongly patterned by education and income levels.[42,43] Third, our data set did not enable us to assess the severity of disease at admission, other conventional risk factors, such as hypertension, diabetes mellitus, obesity, and physical activity,[7,13] nor workplace-related risk factors, such as long working hours and job stress.[9,36,37] In addition, we could not assess the background differences among those admitted to the hospitals with work-related CVD or not. Despite these limitations, the strengths of the present study include a large sample size, one of the largest studies conducted for evaluating the association between occupational class and cardiovascular risk in non-Western settings,[42] and the longest-held occupational class, which may introduce less misclassification.[23,24,27] Therefore, future studies incorporating these limitations, including overtime work, are warranted to understand further how the occupation is associated with the observed socioeconomic patterns in cardiovascular and cerebrovascular health.

Conclusion

In conclusion, the Japanese managerial/professional class appeared to potentially experience higher CHD risk compared with other groups, and their overall life expectancy might not be higher than lower occupational classes. There are some specific causes of death in which managers/professionals have higher mortality—eg, suicide.[44] This pattern appears to reflect the higher prevalence of work-related stress in higher status occupations.[23] Moreover, when we look at overall mortality, the Japanese pattern may buck the trend seen in other developed (Western) societies where high SES groups enjoy a health advantage.[45,46] Our findings may be a potential exception to the theory of "SES as a fundamental cause of disease" advanced by Link and Phelan, ie, no matter the specific pattern of disease in society at any particular point in time, high SES groups still manage to enjoy an overall health advantage.[47]

Author Contributions

Masayoshi Zaitsu: Conceptualization, funding acquisition, resources, formal analysis, writing—original draft, and writing—review and editing. Soichiro Kato: Conceptualization, writing—review and editing. Yongjoo Kim: Writing—review and editing. Takumi Takeuchi: Resources and writing—review and editing. Yuzuru Sato: Writing—review and editing. Yasuki Kobayashi: Funding acquisition, supervision, and writing—review and editing. Ichiro Kawachi: Conceptualization, supervision, and writing—review and editing.

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Disclosures

None.

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ORIGINAL RESEARCH

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Risk of cancer and longest-held occupations in Japanese workers: A multicenter hospital-based case-control study

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Abstract

Objectives: Little is known about the risk of developing various cancers according to occupation and occupational physical activity.

Methods: Using nationwide clinical inpatient data (1984-2017) in Japan, we undertook a multicentered, matched case-control study with regard to the risk of developing various cancers according to occupation and using patients admitted with fractures as controls. Using standardized national occupation and industrial classifications, we first identified the longest-held job for each patient. Using sales workers as the reference group, odds ratios (ORs) and 95% confidence intervals (CIs) were estimated by conditional logistic regression, adjusted for age, admission period, and the admitting hospital, with smoking, alcohol consumption, and lifestyle diseases as covariates. The risk of high and low occupational physical activity was also estimated.

Results: Across all occupations, a reduced risk for all common cancers among males was observed among those occupations associated with high physical activities, such as agriculture. People in these occupations tended to show a lower risk for most cancers, including, for example, prostate cancer (OR 0.58, 95% CI 0.45-0.75) and lung cancer (OR 0.63, 95% CI 0.51-0.76). For females, the breast cancer risk was low in women engaged in agriculture (OR 0.58, 95% CI 0.45-0.75) and in those occupations with high levels of occupational physical activity (OR 0.58, 95% CI 0.52-0.66).

Conclusions: This study revealed differences in cancer risk among diverse occupations in Japan. Specifically, those occupations associated with high levels of physical activity may be associated with a decreased risk of cancer.

KEYWORDS
cancer, occupational activity, risk

1 | INTRODUCTION

Occupations, in particular, are a major social determinant of health.[1] Working is generally recognized as having an effect on human health and well-being; for example, specific occupations can cause harm in the form of malignant neoplasms.[2-4]

Globally, cancer is the second leading cause of death behind cardiovascular diseases, having caused over 8.7 million deaths in 2015.[5] In Japan, cancer is the leading cause of death, with the total incidence of cancer in 2016 being estimated to be 867 408 (501 527 males and 365 881 females).[6] In spite of this, it is thought that about half of all incidences of mortality from cancer in Japan are preventable.[7]

With regard to the role of occupation in the etiology of cancer, occupational exposure to carcinogens as well as occupation-related lifestyle factors can add to the effective risk for cancer.[8]

Previous studies have investigated the association between occupation and cancer mortality.[9-11] But, whether occupational physical activity is associated with a risk of cancer is unclear.[12] In Japan, many working people spend a large proportion of their life in gainful employment. Unfortunately, stemming from a particular Japanese work culture, people's occupational activity may limit their ability to exercise. In several epidemiologic studies, an inverse association between recreational physical activity and cancer was established.[13-15] In comparison, like "the physical activity paradox" for cardiovascular diseases, occupational and recreational physical activity has been associated with different effects on the risk of a particular cancer.[16,17]

The aim of this study was to describe the cancer risk especially associated with occupation, paying attention to the level of occupational physical activity (OPA) in Japanese workers. Using nationwide, multicenter inpatient data, including individual-level clinical data and occupational information, we examined the risk of cancer associated with each occupation.

1.1 | Subjects

1.1.1 | Inpatient Clinico-Occupational Database of Rosai Hospital Group

We used the Inpatient Clinico-Occupational Database of Rosai Hospital Group (ICOD-R), provided by the Japan Organization of Occupational Health and Safety (JOHAS), an independent administrative agency in Japan. Rosai Hospitals now comprise 33 hospitals, located from Hokkaido to Kyushu, in both rural and urban areas in Japan. The database contains medical chart information overseen by physicians, including a clinical history and diagnosis of current and past diseases, pathological information, treatments, and the outcome for every inpatient. The diagnoses are coded according to the International Statistical Classification of Diseases and Related Health Problems, 9th Revision (ICD-9) or 10th Revision (ICD-10). The ICOD-R also includes an occupational history (current and past three jobs), information on lifestyle such as smoking and alcohol habits, and a history of lifestyle-related diseases using interviews and questionnaires completed at the time of admission. Detailed occupational histories were coded using 3-digit codes of the standardized national classification, the Japan Standard Occupational Classification and Japan Standard Industrial Classification, corresponding to the International Standard Industrial Classification and International Standard Occupational Classification. Written informed consent was obtained before patients completed questionnaires, and trained registrars were in charge of registering the data. Registrars are "health information managers", qualified people in Japan. This is quite a unique feature of the database in Japan. The profiles of the inpatients are nationally representative because the Rosai Hospital Group has grown to cover all occupations since the establishment of the Rosai Hospital Group by the Ministry of Labour of Japan in 1949.

2 | METHODS

The study was approved by the ethics committees of The University of Tokyo (No. 10891) and Kanto Rosai Hospital (No 2018-11).

2.1 | Case and control datasets

We obtained an anonymous dataset extracted from ICOD-R with the permission of JOHAS, which included admissions to hospital between 1984 and 2017. We conducted a multicenter, hospital-based matched case-control study. With respect to selection cases and controls, we randomly sampled one control for each cancer case from cases of fractures of the arms and legs (ICD-9, 810-829 and ICD-10, S40-S99), matched for age, sex, period of admission date, and admitting hospital.

The cancer cases were difined by those patients with an inital diagnosis of cancer coded by ICD-9 or ICD-10. The cancer sites were selected according to national statistics in Japan,[6,7,18] with the top most common cancer sites: prostate, breast, kidney, ureter, bladder, esophagus, stomach, liver, pancreas, colon, and lung. The prevalence of these cancers in our dataset was almost identical to that recorded by Japanese national statistics.[19]

2.2 | Occupation categories and occupational physical activity

To evaluate the odds ratio of each occupation, we chose the longest-held job of each patient from their occupational history.[11,20] Occupational categories were categorized into 12 categories according to the middle classification of the Japan Standard Occupational Classification of 2013. These categories were based on the International Standard Classification of Occupations. The twelve occupational categories were as follows: administrative and managerial; professional; clerical; sales; services; security; agriculture; manufacturing; transport; construction and mining; carrying, cleaning and packing; and others.

We also analyzed several additional categories. The occupational groups with high or low levels of OPA were defined based on information on their accelerometer-derived

occupational activities, modified by the National Health and Nutrition Examination Survey of 2003-2004 (NHANES).[21] High physical activity groups included agriculture, construction and mining, and carrying, cleaning and packing. The low activity groups included administrative and managerial, professional, and clerical.

2.3 | Statistical analysis

Conditional regression analysis was used for the estimation of odd ratios (ORs), with 95% confidence intervals (95% CIs), for each occupational category in relation to the risk for each cancer. The sales workers group was selected as a reference category in accordance with a previous study.[22] The risks for high and low OPA groups were estimated compared to the other remaining cases (eg, the low OPA group vs. a reference group of all cases except the low OPA group). We conducted separate analyses for males and females due to the etiology of cancer.[23] Age was categorized every 5 years. The period of admission was categorized into four study periods (1984-1990, 1991-2000, 2001-2010, 2011-2017) and matched into pairs. Models were adjusted for age, sex, period of admission, and admission hospital. Smoking, consumption of alcohol, and lifestyle-related diseases (hypertension, hyperlipidemia, hyperuricemia, diabetes mellitus, and obesity) were included as covariates. For smoking, we used the Brinkman Index: calculated as the number of cigarettes smoked per day multiplied by the number of years smoked. Alpha was set at 0.05, and all *P*-values were two-sided. All analyses were conducted using STATA/MP15.0 (Stata Corp LP).

3 | RESULTS

The total number of inpatient cases registered in the ICOD-R from 1984 to 2017 comprised 6 526 387. Of these, completed data were available for 6 309 852 cases, which included birthday, sex, ICD-9, or ICD-10 code, history of smoking and alcohol consumption. Of these cases, 4 186 750 were first-time admissions of the initial admission cases, while occupational information was available for 1 843 672 cases. Cancers for the 57 913 cases included prostate, breast, kidney, ureter, bladder, esophagus, stomach, liver, pancreas, colon and lung. The demographics of each cancer are shown in Table 1.

The average age of breast cancer patients was the lowest of all cancer sites (56.2 ± 12.8 years; Table 1). The mean age of ureter and bladder cancer patients was over 70 years (70.9 ± 9.6, 70.0 ± 10.7 years, respectively). With regard to occupational sites, the mean age of cancer patients working in agriculture was from 69.1 ± 12.6-77.7 ± 8.9 years depending on cancer sites, which was the highest for all the occupational categories. The mean age of patients in the high OPA group (63.5 ± 13.3-72.9 ± 9.0 years) was greater than that of patients in the low OPA group (53.8 ± 12.2-70.4 ± 10.5 years), except for liver cancer.

For males, the sample size for the regression analysis was large enough to handle using nine variables. For females, the number of cases about OPA category was large enough, though each occupational category with several cancer cases was under 90 cases (number of variables times 10).

Table 2 shows the Brinkman Index, amount of alcohol consumed and number of patients with a history of lifestyle-related diseases for each industrial category. The number of patients who regularly smoked or took alcohol tended to be fewer in agriculture.

Agriculture was significantly associated with reduced risks for most cancers in males (Table 3). In this category, the adjusted ORs were low, with a significant difference observed for all cancer sites. They ranged from 0.46 (95% CI 0.27-0.78) for ureter carcinoma to 0.63 (95% CI 0.55-0.74) for carcinoma in the stomach (0.63 95% CI 0.46-0.88), liver (0.63 95% CI 0.46-0.88), and lung (0.63 95% CI 0.51-0.76). The high OPA group also tended to be associated with a lower risk for all cancers, ranging from 0.58 (95% CI 0.52-0.66) for prostate cancer to 0.79 (95% CI 0.72-0.86) for lung cancer. However, no obvious effect except for breast cancer was detected in female cases. The odds of breast cancer for those in agriculture (0.58 95% CI 0.45-0.75) and the high OPA group (0.58 95% CI 0.52-0.66) were significantly lower (Table 4).

As a whole in males, an overall reduced risk for all cancers was associated with those occupations related to high OPA. In females, a reduced risk for breast cancer showed a similar tendency: an association with occupations characterized by high OPA.

4 | DISCUSSION

4.1 | Change of occupational risk in a historical transition

In general, workers are engaged in their jobs for about 40 hours per week, which means that they spend one-fourth of their time in job-related activities. Moreover, many Japanese companies have conventionally adopted the lifetime employment system: a promise by a company to an employee that they will have a job for their whole working life, as is customary in Japanese society. Therefore, most workers' lifetime physical activity in Japan can be defined by an OPA.

In Japan, one of the main changes observed in the employment sector in recent years has been the decline in the proportion of the population working in agriculture. In comparison, the proportion of workers engaged in the tertiary sector, including sales and services, is increasing rapidly. As a result, physical activity derived from an occupation has tended to diminish. Such major changes have been observed from the

TABLE 1 Sex and age distribution of all cancer cases and controls in each occupational category

Occupational category n=	ALL		Prostate		Breast		Kidney		Ureter		Bladder	
	Case	Control	Case	Control	Case	Control	Case	Control	Case	Control	Case	Control
	57913	57913	3429	3429	5093	5093	1450	1450	1013	1013	5964	5964
ALL												
n = (male:female)	41 957:15 956	41 955:15 956	3429:0	3428:0	75:5018	75:5018	1136:314	1136:314	828:185	828:185	5314:650	5314:650
Age(mean ± SD)	66.7 ± 11.5	66.8 ± 11.8	66.4 ± 8.8	66.4 ± 9.11	56.2 ± 12.8	56.4 ± 12.9	63.3 ± 11.9	63.4 ± 12.2	70.9 ± 9.6	71.0 ± 10.2	70.0 ± 10.7	70.1 ± 11.0
Administrative and managerial												
n = (male:female)	2773:235	2587:248	225:0	226:0	3:48	7:61	84:4	49:6	63:4	62:5	376:19	342:14
Age(mean ± SD)	68.9 ± 10.0	71.1 ± 10.0	66.8 ± 8.3	68.7 ± 9.0	58.4 ± 12.7	64.7 ± 12.7	65.5 ± 11.1	68.3 ± 10.7	72.4 ± 10.2	73.7 ± 8.1	70.4 ± 10.3	73.3 ± 9.5
Professionals												
n = (male:female)	4656:2263	4263:2507	501:0	336:0	19:910	12:994	167:42	133:52	93:16	83:24	621:92	567:78
Age(mean ± SD)	64.5 ± 12.8	63.5 ± 13.1	64.5 ± 9.1	64.2 ± 9.5	53.3 ± 12.2	51.6 ± 12.3	59.8 ± 12.8	60.9 ± 13.6	70.4 ± 10.5	69.3 ± 11.9	69.4 ± 11.9	68.9 ± 12.0
Clerical												
n = (male:female)	5788:3695	4549:3477	600:0	366:0	11:1466	5:1234	194:77	139:63	135:29	90:31	762:127	584:126
Age(mean ± SD)	64.3 ± 12.4	64.7 ± 12.6	65.3 ± 9.3	66.8 ± 9.2	53.9 ± 12.2	53.8 ± 11.3	61.7 ± 12.5	63.2 ± 11.9	69.5 ± 10.5	71.4 ± 10.9	69.2 ± 11.1	69.3 ± 11.7
Sales												
n = (male:female)	4726:2127	4000:2042	367:0	343:0	5:683	10:619	139:38	125:40	90:34	85:23	626:95	494:92
Age(mean ± SD)	65.1 ± 11.7	65.8 ± 11.9	64.9 ± 8.5	65.5 ± 9.8	55.8 ± 13.2	57.0 ± 12.7	62.1 ± 11.8	62.4 ± 11.9	60.7 ± 10.7	70.5 ± 10.3	68.5 ± 11.2	69.2 ± 11.2
Services												
n = (male:female)	2678:1476	1492:2663	100:0	121:0	5:750	1:812	37:55	43:59	40:35	23:31	156:111	201:105
Age(mean ± SD)	64.2 ± 11.1	65.2 ± 11.7	65.7 ± 8.0	64.9 ± 7.7	57.5 ± 11.8	58.5 ± 12.8	64.1 ± 10.8	63.4 ± 11.9	68.4 ± 9.2	68.9 ± 9.9	68.0:10.8	69.9 ± 10.7
Security												
n = (male:female)	987:25	951:23	93:0	74:0	1:11	3:14	16:0	24:1	28:0	9:0	125:2	116:1
Age(mean ± SD)	67.8 ± 10.6	65.2 ± 11.6	64.9 ± 8.4	64.3 ± 9.1	55.8 ± 16.1	47.3 ± 13.9	66.0 ± 10.8	58.2 ± 13.9	69.8 ± 12.1	68.7 ± 9.9	69.3 ± 8.1	68.0 ± 11.7
Agriculture												
n = (male:female)	2465:1270	3517:1375	183:0	274:0	3:153	3:228	55:22	81:22	46:22	83:21	299:69	458:67
Age(mean ± SD)	75.2 ± 9.9	74.2 ± 10.8	71.4 ± 9.3	71.9 ± 9.3	70.4 ± 13.4	68.9 ± 13.9	71.3 ± 10.6	69.1 ± 12.6	77.6 ± 8.3	76.9:9.4	77.7 ± 8.9	76.4 ± 9.4
Manufacturing												
n = (male:female)	8824:2194	9197:2166	661:0	747:0	12:609	16:659	213:42	248:39	176:30	189:27	1160:72	1172:105
Age(mean ± SD)	67.7 ± 10.5	67.4 ± 10.7	67.0 ± 8.3	66.3 ± 8.7	60.0 ± 12.5	59,5 ± 12.5	64.7 ± 11.1	64.3 ± 11.9	71.1 ± 7.6	79.7 ± 10.0	70.7 ± 9.7	69.8 ± 10.6
Transport												
n = (male:female)	4323:158	4422:150	297:0	374:0	4:62	8:52	65:2	120:3	60:1	89:1	526:4	547:5
Age(mean ± SD)	67.8 ± 9.9	66.5 ± 10.1	67.8 ± 7.3	65.0 ± 7.7	53.6 ± 13.5	58.3 ± 13.1	64.3 ± 10.4	61.8 ± 11.9	72.3 ± 7.7	68.9 ± 7.9	69.8 ± 10.1	68.6 ± 9.8
Construction and mining												
n = (male:female)	4.515:121	5289:111	279:0	423:0	8:12	8:18	112:2	131:4	80:3	89:1	512:4	621:6
Age(mean ± SD)	68.1 ± 19.3	67.1 ± 10.5	67.6 ± 8.8	65.3 ± 8.7	62.6 ± 12.9	64.4 ± 7.8	63.4 ± 12.3	61.6 ± 10.4	70.4 ± 7.8	71.2 ± 9.3	69.4 ± 9.9	68.4 ± 10.8
Carrying, cleaning and packing												
n = (male:female)	1329:1191	1608:1152	89:0	141:0	4:308	2:322	34:30	43:23	16:11	24:20	143:55	201:50
Age(mean ± SD)	66.1 ± 10.7	65.3 ± 10.9	68.6 ± 9.7	66.3 ± 7.9	60.1 ± 11.9	58.1 ± 12.8	63.2 ± 9.2	64.3 ± 11.9	68.2 ± 9.1	70.7 ± 10.5	68.4 ± 9.6	69.1 ± 10.7
Other												
n = (male:female)	103:16	80:19	1:0	4:0	0:6	0:5	0:0	0:1	1:0	3:0	8:0	11:1
Age(mean ± SD)	77.5 ± 9.3	79.4 ± 9.9	—	78.5 ± 2.5	63.3 ± 13.8	64.4 ± 17.7	—	—	—	69.7 ± 10.2	78.1 ± 7.6	85.1 ± 4.1
Occupational physical activity group												
High activity[†]												
n = (male:female)	8309:2582	10 414:2638	551:0	838:0	15:473	13:568	201:54	255:49	142:36	196:42	954:128	1280:123
Age(mean ± SD)	60.1 ± 10.9	69.4 ± 11.4	69.1 ± 9.3	67.6 ± 9.4	63.5 ± 13.3	62.7 ± 14.1	65.8 ± 11.6	64.7 ± 11.9	72.9 ± 9.0	73.6 ± 9.9	72.1 ± 10.3	71.5 ± 10.9
Low activity [‡]												
n = (male:female)	13 217:6193	11 399:6232	1359:0	928:0	33:2424	24:2289	445:123	321:122	291:49	235:60	1759:238	1493:218
Age(mean ± SD)	65.1 ± 12.3	65.3 ± 12.7	65.3 ± 9.1	66.4 ± 9.5	53.8 ± 12.2	53.2 ± 12.0	61.5 ± 12.6	64.9 ± 12.7	70.4 ± 10.5	71.2 ± 10.8	69.4 ± 11.3	69.9 ± 11.6

Note: When only one case was included in a column, age was not indicated to avoid any chance of patient identification.

SD, standard deviation

[†]High activity group included agriculture, construction and mining, and carrying, cleaning and packing.

[‡]Low activity group included administrative and managerial; professional and clerical support.

Esophagus		Stomach		Liver		Pancreas		Colon		Lung	
Case	Control	Case	Control	Case	Control	Case	Control	Case	Control	Case	Control
2414	2414	11 839	11 839	2637	2637	3056	3056	12 470	12 470	8548	8548
2225:189	2225:189	9270:2569	9270:2569	2032:605	2032:605	2181:875	2181:875	8769:3701	8769:3701	6698:1850	6698:1850
68.6 ± 9.33	68.6 ± 9.7	67.4 ± 11.3	67.4 ± 11.5	66.8 ± 10.8	66.8 ± 11.1	68.9 ± 10.4	68.9 ± 10.6	66.7 ± 11.5	66.7 ± 11.7	68.5 ± 10.3	68.5 ± 10.7
155:2	158:3	570:42	595:35	130:12	117:13	145:11	139:16	591:63	524:65	398:30	368:30
70.1 ± 7.8	71.0 ± 9.6	68.5 ± 10.0	70.9 ± 10.4	68.7 ± 10.2	69.9 ± 10.1	69.7 ± 9.9	72.5 ± 9.5	68.6 ± 10.2	70.6 ± 9.9	60.7 ± 9.3	72.3 ± 9.4
201:7	232:27	998:306	948:372	214:66	204:86	248:103	226:94	1040:495	874:543	554:225	648:237
68.4 ± 9.8	66.9 ± 10.1	65.8 ± 12.9	65.1 ± 12.7	67.2 ± 12.2	65.2 ± 11.2	68.2 ± 11.1	66.5 ± 11.4	64.9 ± 12.4	64.4 ± 12.4	67.1 ± 11.6	66.3 ± 11.5
289:33	220:39	1272:513	998:563	269:115	210:111	274:170	230:168	1179:794	970:770	802:371	738:372
67.4 ± 9.8	69.2 ± 10.9	65.9 ± 11.8	65.8 ± 12.3	65.7 ± 11.3	66.5 ± 11.8	68.2 ± 10.6	67.9 ± 10.9	65.2 ± 12.0	65.1 ± 12.3	66.6 ± 10.9	67.4 ± 11.2
254:23	212:26	1038:309	898:312	204:86	203:86	273:125	195:137	1070:505	824:493	660:222	611:221
67.5 ± 10.0	67.3 ± 10.4	65.0 ± 11.5	66.3 ± 11.7	67.0 ± 10.2	66.9 ± 12.2	68.1 ± 10.1	67.5 ± 10.5	65.3 ± 11.6	66.0 ± 11.9	66.7 ± 10.3	67.4 ± 10.7
115:50	87:22	301:423	332:432	81:136	69:105	78:135	73:136	318:625	324:620	239:358	218:347
65.2 ± 8.8	67.7 ± 10.2	65.5 ± 11.0	66.3 ± 11.1	65.7 ± 11.1	67.6 ± 9.9	65.5 ± 10.1	69.2 ± 10.0	65.1 ± 10.6	65.8 ± 11.3	66.0 ± 9.6	67.4 ± 10.1
49:1	50:0	244:4	231:2	45:1	55:0	52:1	41:1	197:5	185:3	137:0	163:1
68.5 ± 9.3	64.3 ± 9.2	67.6 ± 10.5	65.7 ± 11.4	68.8 ± 10.2	63.7 ± 10.2	68.6 ± 11.4	64.5 ± 11.6	68.3 ± 12.1	64.3 ± 12.6	68.6 ± 10.2	67.7 ± 10.1
128:20	185:19	614:308	792:268	114:57	167:67	147:100	200:115	464:346	682:366	412:173	592:202
73.8 ± 9.5	72.9 ± 9.6	75.8 ± 9.6	74.3 ± 10.8	72.1 ± 10.2	72.8 ± 10.6	76.1 ± 10.3	75.9 ± 10.2	75.7 ± 10.4	74.2 ± 11.1	75.9 ± 8.6	75.1 ± 10.1
491:30	500:35	1941:401	1973:346	411:80	447:80	433:129	434:133	1747:513	1995:505	1579:283	1456:242
68.8 ± 9.2	68.9 ± 8.6	67.6 ± 10.3	67.7 ± 10.6	67.5 ± 10.4	66.6 ± 10.4	68.9 ± 9.2	68.9 ± 10.1	66.9 ± 11.1	67.2 ± 10.7	68.6 ± 9.8	68.5 ± 9.9
209:1	229:1	990:24	979:18	249:2	228:3	240:10	230:10	907:37	898:32	756:15	720:25
69.4 ± 8.3	66.9 ± 9.0	67.7 ± 9.7	66.7 ± 10.3	65.4 ± 10.6	63.8 ± 10.6	67.5 ± 9.7	67.2 ± 8.9	66.4 ± 10.1	65.9 ± 10.4	68.5 ± 9.4	67.7 ± 9.7
240:3	260:1	968:25	1169:25	248:7	241:7	221:12	307:6	936:31	1139:27	910:22	902:16
68.6 ± 8.4	68.3 ± 9.1	67.7 ± 10.9	66.7 ± 10.5	64.7 ± 9.7	66.1 ± 10.8	69.2 ± 9.8	68.2 ± 10.4	68.0 ± 10.7	66.3 ± 11.2	69.1 ± 9.9	68.3 ± 10.2
85:19	88:15	313:210	341:193	62:43	88:46	65:77	81:59	297:286	333:273	221:148	266:155
67.8 ± 8.9	67.1 ± 7.9	66.3 ± 10.9	65.9 ± 10.4	64.7 ± 10.9	65.8 ± 10.4	68.5 ± 9.6	67.3 ± 9.2	66.6 ± 10.2	64.4 ± 10.5	67.8 ± 9.7	66.9 ± 9.9
9:0	4:1	21:4	14:3	5:0	3:1	5:2	5:0	23:1	20:5	30:3	16:2
74.0 ± 12.8	85.2 ± 2.9	78.9 ± 9.0	78.8 ± 9.1	70.0 ± 8.1	82.8 ± 3.8	81.6 ± 8.2	81.2 ± 7.0	77.3 ± 8.9	76.6 ± 9.8	78.6 ± 6.7	82.6 ± 10.6
453:42	533:35	1895:543	2302:486	424:107	496:120	433:180	588:180	1697:663	2154:666	1543:343	1760:373
69.9 ± 9.1	69.7 ± 9.4	60.4 ± 11.3	69.4 ± 11.3	67.1 ± 10.7	68.6 ± 11.1	71.8 ± 10.6	71.2 ± 10.8	70.3 ± 11.2	68.9 ± 11.8	70.9 ± 10.1	70.6 ± 10.7
645:42	610:69	2840:861	2541:970	613:193	531:210	667:284	595:278	2810:1352	2368:1378	1754:626	1754:639
68.3 ± 9.4	68.7 ± 10.4	66.3 ± 11.8	66.5 ± 12.3	66.8 ± 11.5	66.6 ± 11.4	68.5 ± 10.7	68.2 ± 11.0	65.6 ± 11.9	65.7 ± 12.2	67.5 ± 10.9	67.8 ± 11.2

TABLE 2 Distribution of life-related diseases for each occupational category

Occupational category	Brinkman Index[‡] Median (IQR[†]25%:75%)		Alcohol (g/day) Median (IQR[†]25%:75%)		Hypertension n = (%)		Hyperlypidemia n = (%)		Hyperuricemia n = (%)		Diabetes n = (%)		Obesity n = (%)	
	Case	Control	Case	Control	Case	Control	Case	Control	Case	Control	Case	Control	Case	Control
All	410 (0:840)	250 (0:740)	23.5 (0:75.0)	0 (0:600)	20 099 (34.7)	19 461 (33.6)	6726 (11.6)	6866 (11.8)	1769 (3.1)	1778 (3.1)	8683 (15.0)	9206 (15.9)	7451 (12.9)	6912 (11.9)
Administrative and managerial	640 (200:1020)	460 (0:920)	48.0 (0:90.0)	32.4 (0:82.0)	1224 (40.7)	1080 (38.1)	433 (14.4)	470 (16.6)	173 (5.7)	121 (4.3)	602 (20.0)	645 (22.8)	534 (17.7)	495 (17.5)
Professionals	240 (0:700)	65 (0:540)	80.0 (0:60.0)	0 (0:40.0)	2292 (33.1)	2075 (30.6)	1134 (16.4)	1162 (17.2)	283 (4.1)	286 (4.2)	990 (14.3)	869 (12.8)	1105 (15.9)	946 (13.9)
Clerical	225 (0:740)	20 (0:540)	55.0 (0:62.5)	0 (0:40.0)	3059 (32.3)	2591 (32.3)	1422 (15.0)	1325 (16.5)	308 (3.3)	231 (2.9)	1308 (13.8)	1038 (12.9)	1404 (14.8)	1150 (14.3)
Sales	400 (0:840)	220 (0:720)	23.0 (0:74.0)	30.0 (0:60.0)	2349 (34.3)	2048 (33.9)	821 (11.9)	703 (11.6)	247 (3.6)	250 (4.1)	1104 (16.1)	1059 (17.5)	971 (14.2)	773 (12.8)
Services	100 (0:620)	0 (0:450)	0 (0:47.0)	0 (0:32.0)	1323 (31.9)	1372 (33.0)	422 (10.2)	461 (11.1)	67 (1.6)	77 (1.9)	498 (12.0)	670 (16.1)	509 (12.3)	504 (12.1)
Security	600 (200:900)	480 (3:900)	50.5 (0:86.0)	28.0 (0:760)	408 (40.3)	332 (34.1)	154 (15.2)	169 (17.4)	43 (4.3)	16 (1.6)	166 (16.4)	184 (18.9)	176 (17.4)	187 (19.2)
Agriculture	198 (0:840)	25 (0:775)	0 (0:70.0)	0 (0:58.0)	1455 (38.9)	1730 (35.4)	282 (7.6)	298 (6.1)	69 (1.9)	51 (1.0)	527 (14.1)	770 (15.7)	246 (6.6)	258 (5.3)
Manufacturing	480 (0:855)	330 (0:760)	30.0 (0:76.0)	90.0 (0:64.0)	3751 (34.1)	3986 (35.1)	1027 (9.3)	1195 (10.5)	283 (2.6	330 (2.9)	1577 (14.3	1710 (15.1)	1273 (11.6)	1142 (10.1)
Transport	705 (300:1000)	520 (70:900)	54.0 (0:90.0)	40.0 (0:80.0)	1696 (37.9)	1604 (35.1)	423 (9.4)	471 (10.3)	127 (2.8)	197 (4.3)	802 (17.9)	1029 (22.5)	539 (12.0)	519 (12.9)
Construction and mining	675 (300:900)	560 (85:880)	54.0 (0:90.0)	36.0 (0:80.0)	1673 (36.1)	1783 (33.0)	339 (7.3)	362 (6.7)	115 (2.5)	147 (2.7)	756 (16.3)	684 (16.0)	404 (8.7)	515 (9.5)
Carrying, cleaning and packing	225 (0:740)	120 (0:600)	0 (0:60.0)	0 (0:46.0)	822 (32.7)	818 (29.6)	260 (10.3)	247 (8.9)	50 (2.0)	69 (2.5)	338 (13.4)	348 (12.6)	286 (11.4)	346 (12.5)
Other	580 (154:940)	560 (0:1140)	44.0 (0:85.5)	60.0 (0:104.0)	47 (39.5)	42 (42.4)	9 (7.6)	3 (3.0)	4 (3.4)	3 (3.0)	15 (12.6)	20 (20.2)	6 (5.0)	5 (5.1)
Occupational physical activity group														
High activity group[§]	490 (0:900)	350 (0:800)	28.0 (0:80.0)	0 (0:68.0)	3950 (36.3)	4331 (33.2)	881 (8.1)	907 (6.9)	234 (2.2)	267 (2.1)	1621 (14.9)	1982 (15.2)	936 (8.6)	1119 (8.6)
Low activity group [¶]	370 (0:800)	110 (0:600)	20.0 (0:70.0)	0 (0:50.0)	3614 (34.6)	5746 (32.6)	1537 (14.7)	2957 (16.8)	391 (3.8)	638 (3.6)	1673 (16.0)	2552 (14.5)	1629 (15.6)	2591 (14.7)

[†]IQR:Interquartile range.

[‡]Brinkman Index: the number of cigarettes smoked per day multiplied by the number of years smoked.

[§]High activity group included agriculture; construction and mining, and carrying, cleaning and packing.

[¶]Low activity group included administrative and managerial; professional and clerical support.

TABLE 3 Odds ratio of each occupational category to cancer in males

	Prostate	Kidney	Ureter	Bladder	Esophagus	Stomach	Liver	Pancreas	Colon	Lung
Numbers of cases	**3429**	**1136**	**828**	**5314**	**2225**	**9270**	**2032**	**2181**	**8769**	**6698**
Occupational category (sales as a reference)										
Administrative and managerial	1.02 (0.81-1.92)	1.45 (0.93-2.24)	0.99 (0.61-1.61)	0.84 (0.69-1.02)	0.81 (0.59-1.09)	0.81 (0.69-0.93)	1.07 (0.77-1.49)	0.69 (0.50-0.94)	0.87 (0.75-1.02)	0.96 (0.79-1.19)
	.862	.099	.975	.085	.172	.005**	.686	.017*	.082	.751
Professionals	1.32 (1.07-1.63)	1.12 (0.78-1.59)	1.09 (0.70-1.69)	0.90 (0.76-1.07)	0.68 (0.52-0.91)	0.96 (0.84-1.09)	1.10 (0.83-1.46)	0.81 (0.62-1.05)	0.94 (0.82-1.070	0.90 (0.76-1.07)
	.008**	.545	.693	.247	.008**	.501	.500	.120	.344	.261
Clerical	1.45 (1.19-1.78)	1.15 (0.81-1.63)	1.46 (0.96-2.22)	1.06 (0.90-1.26)	1.00 (0.76-1.32)	1.12 (0.98-1.26)	1.29 (0.98-1.69)	0.85 (0.65-1.09)	0.95 (0.84-1.08)	1.11 (0.94-1.32)
	.000**	.425	.075	.458	.972	.086	.069	.209	.434	.206
Sales (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
	—	—	—	—	—	—	—	—	—	—
Services	0.73 (0.54-1.00)	0.74 (0.44-1.24)	1.59 (0.85-2.96)	0.65 (0.51-0.83)	0.99 (0.69-1.42)	0.80 (0.67-0.96)	1.14 (0.78-1.69)	0.78 (0.53-1.14)	0.77 (0.64-0.93)	1.14 (0.89-1.45)
	.051	.255	.145	.001**	.983	.019*	.496	.194	.006**	.289
Security	1.10 (0.78-1.55)	0.55 (0.27-1.12)	2.91 (1.17-7.26)	0.81 (0.61-1.08)	0.79 (0.50-1.26)	0.89 (0.72-1.09)	0.81 (0.52-1.29)	0.85 (0.54-1.35)	0.83 (0.67-1.03)	0.80 (0.61-1.07)
	.578	.101	.022*	.158	.331	.282	.397	.499	.103	.131
Agriculture	0.58 (0.45-0.75)	0.58 (0.37-0.93)	0.46 (0.27-0.78)	0.49 (0.40-0.61)	0.51 (0.37-0.70)	0.63 (0.55-0.74)	0.63 (0.46-0.88)	0.49 (0.36-0.66)	0.49 (0.42-0.58)	0.63 (0.51-0.76)
	.000**	.022*	.004**	.000**	.000**	.000**	.006**	.000**	.000**	.000**
Manufacturing	0.77 (0.64-0.93)	0.77 (0.55-1.06)	0.83 (0.56-1.23)	0.79 (0.69-0.92)	0.76 (0.61-0.97)	0.85 (0.76-0.96)	0.87 (0.69-1.12)	0.67 (0.53-0.85)	0.67 (0.59-0.75)	1.05 (0.91-1.22)
	.009**	.106	.362	.002**	.029	.006**	.281	.001**	.000**	.478
Transport	0.73 (0.58-0.91)	0.57 (0.38-0.85)	0.58 (0.37-0.94)	0.74 (0.62-0.88)	0.69 (0.53-0.93)	0.85 (0.75-0.78)	0.98 (0.74-1.29)	0.72 (0.55-0.94)	0.76 (0.67-0.87)	0.93 (0.78-1.10)
	.005**	.006**	.026**	.001**	.012*	.000**	.879	.014**	.000**	.403
Construction and mining	0.58 (0.47-0.73)	0.74 (0.52-1.07)	0.81 (0.52-1.26)	0.63 (0.53-0.75)	0.66 (0.50-0.87)	0.68 (0.61-0.78)	0.98 (0.75-1.29)	0.49 (0.38-0.64)	0.62 (0.54-0.70)	0.92 (0.78-1.08)
	.000**	.114	.343	.000**	.003**	.000**	.891	.000**	.000**	.328
Carrying, cleaning and packing	0.58 (0.43-0.80)	0.71 (0.42-1.20)	0.58 (0.28-1.21)	0.57 (0.44-0.73)	0.81 (0.55-1.19)	0.77 (0.64-0.92)	0.74 (0.50-1.08)	0.52 (0.35-0.77)	0.69 (0.57-0.82)	0.71 (0.56-0.89)
	.001**	.198	.149	.000**	.287	.005**	.126	.000**	.000**	.003**
Other	0.20 (0.02-1.85)	N/A	0.11 (0.01-1.19)	0.51 (0.19-1.29)	1.57 (0.39-6.37)	1.20 (0.60-2.42)	1.45 (0.33-6.40)	0.51 (0.12-2.11)	0.80 (0.43-1.48)	2.28 (1.13-4.61)
	.156	N/A	.070	.157	.527	.600	.619	.351	.481	.021*
Occupational activity group (the other workers as a reference)										
High activity[†]	0.58 (0.52-0.66)	0.74 (0.60-0.93)	0.65 (0.50-0.83)	0.67 (0.61-0.73)	0.77 (0.65-0.90)	0.75 (0.69-0.80)	0.80 (0.69-0.94)	0.65 (0.56-0.75)	0.72 (0.67-0.77)	0.79 (0.72-0.86)
	.000**	.009**	.001**	.000**	.001**	.000**	.000**	.000**	.000**	.000**
Low activity[‡]	1.74 (0.57-1.93)	1.60 (1.33-1.93)	1.45 (1.16-1.79)	1.29 (1.18-1.41)	1.09 (0.94-1.26)	1.21 (1.13-1.29)	1.28 (1.11-1.48)	1.19 (1.04-1.37)	1.03 (1.22-1.39)	1.08 (0.99-1.17)
	.000**	.000**	.001**	.000**	.215	.000**	.001**	.013*	.000**	.104

Note: Odds ratios were estimated by conditional logistic regression matched for age, sex, admission period, and admitting hospital.

The upper row shows odds ratios (95% confidence interval) against sales workers as a reference (ref).

The lower row shows *P*-values of <.01** or <.05* were considered to be statistically significant

NA: Data was not available for a number of cases, making this category too small.

[†]High activity group included agriculture, construction and mining, and carrying, cleaning and packing

[‡]Low activity group included administrative and managerial, and professional and clerical support.

TABLE 4 Odds ratio of each occupational category to cancer in females

	Breast	Kidney	Ureter	Bladder	Esophagus	Stomach	Liver	Pancreas	Colon	Lung
Numbers of cases	**5018**	**314**	**185**	**650**	**189**	**2569**	**605**	**875**	**3701**	**1850**
Occupational category (sales as a reference)										
Administrative and managerial	0.68 (0.17-2.70)	0.68 (0.17-2.74)	0.52 (0.12-2.25)	1.32 (0.59-2.97)	5.68 (0.62-52.11)	1.13 (0.69-1.83)	0.77 (0.31-1.94)	0.78 (0.34-1.78)	0.95 (0.66-1.37)	0.97 (0.55-1.71)
	.862	.592	.382	.498	.124	.629	.578	.550	.798	.911
Professionals	1.32 (1.07-1.63)	0.89 (0.47-1.68)	0.34 (0.13-0.86)	1.15 (0.75-1.77)	0.21 (0.05-0.80)	0.84 (0.67-1.05)	0.83 (0.53-0.1.29)	1.29 (0.89-1.89)	0.89 (0.75-1.06)	0.97 (0.74-1.27)
	.008**	.716	.024*	.532	.023*	.123	.413	.186	.183	.836
Clerical	1.45 (1.19-1.78)	1.43 (0.78-2.63)	0.49 (0.22-1.10)	1.03 (0.69-1.55)	1.23 (0.55-2.73)	0.91 (0.74-1.11)	1.01 (0.67-1.54)	1.17 (0.84-1.65)	1.00 (0.86-1.18)	1.09 (0.86-1.39)
	.000**	.252	.084	.871	.610	.345	.946	.356	.958	.484
Sales (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
	—	—	—	—	—	—	—	—	—	—
Services	0.73 (0.54-1.00)	1.01 (0.55-1.87)	0.69 (0.33-1.49)	0.93 (0.62-1.39)	3.04 (1.21-7.65)	0.97 (0.69-1.19)	1.19 (0.79-1.81)	1.09 (0.77-1.56)	0.97 (0.82-1.15)	0.92 (0.72-1.18)
	.051	.972	.350	.728	.018*	.791	.409	.612	.738	.527
Security	1.10 (0.78-1.55)	N/A	N/A	2.59 (0.23-29.71)	N/A	2.41 (0.43-13.41)	N/A	0.99 (0.06-16.37)	1.59 (0.38-6.73)	N/A
	.578	N/A	N/A	.443	N/A	.315	N/A	.997	.528	N/A
Agriculture	0.58 (0.45-0.75)	0.96 (0.43-2.19)	0.61 (0.25-1.52)	1.01 (0.60-1.68)	2.18 (0.77-6.21)	1.26 (0.98-1.62)	0.83 (0.51-1.35)	0.94 (0.62-1.43)	0.93 (0.75-1.15)	0.91 (0.67-1.24)
	.000**	.935	.290	.981	.143	.062	.446	.788	.500	.559
Manufacturing	0.77 (0.64-0.93)	1.02 (0.53-1.97)	0.78 (0.35-1.77)	0.70 (0.45-1.08)	1.18 (0.51-2.73)	1.21 (0.98-1.51)	1.00 (0.64-1.58)	1.11 (0.77-1.59)	0.99 (0.83-1.19)	1.21 (0.93-1.58)
	.009**	.943	.555	.107	.700	.077	.995	.576	.921	.156
Transport	0.73 (0.58-0.91)	0.68 (0.10-4.57)	0.99 (0.04-23.94)	0.61 (0.15-2.53)	33.9 (0.77-1487.95)	1.26 (0.66-2.41)	0.63 (0.09-4.23)	1.09 (0.43-2.77)	1.15 (0.69-1.88)	0.48 (0.24-0.97)
	.005**	.693	.997	.501	.068	.477	.637	.857	.590	.041*
Construction and mining	0.58 (0.47-0.73)	0.43 (0.06-2.72)	2.73 (0.24-31.20)	0.73 (0.19-2.73)	21.06 (0.78-569.29)	1.06 (0.58-1.91)	0.72 (0.24-2.16)	2.15 (0.77-5.98)	1.11 (0.69-1.88)	1.21 (0.61-2.42)
	.000**	.368	.418	.639	.07	.853	.555	.144	.590	.577
Carrying, cleaning and packing	0.58 (0.43-0.80)	1.34 (0.63-2.86)	0.31 (0.12-0.78)	1.10 (0.67-1.80)	1.78 (0.66-4.82)	1.09 (0.85-1.42)	0.93 (0.54-1.60)	1.42 (0.92-2.21)	1.11 (0.64-1.91)	0.95 (0.69-1.29)
	.001**	.448	.014*	.703	.257	.469	.785	.116	.901	.741
Other	0.20 (0.02-1.85)	N/A	N/A	N/A	N/A	1.46 (0.31-6.81)	N/A	N/A	0.20 (0.02-1.75)	2.07 (0.28-15.17)
	.156	N/A	N/A	N/A	N/A	.629	N/A	N/A	.147	.472
Occupational activity group (the other workers as a reference)										
High activity[†]	0.58 (0.52-0.66)	1.08 (0.67-1.73)	0.77 (0.46-1.29)	1.11 (0.82-1.49)	1.56 (0.87-2.79)	1.18 (1.02-1.37)	0.85 (0.63-1.17)	1.06 (0.82-1.38)	1.00 (0.88-1.14)	0.92 (0.78-1.11)
	.000**	.742	.328	.510	.132	.026*	.321	.634	.964	.419
Low activitys[‡]	1.74 (0.57-1.93)	1.09 (0.75-1.57)	0.65 (0.39-1.09)	1.20 (0.93-1.55)	0.55 (0.34-0.92)	0.82 (0.72-0.92)	0.91 (0.70-1.17)	1.08 (0.88-1.33)	0.97 (0.88-1.07)	1.05 (0.91-1.22)
	.000**	.651	.102	.151	.022*	.001**	.448	.454	.531	.493

Note: Odds ratios were estimated by conditional logistic regression matched for age, sex, admission period, and admitting hospital.

The upper row shows odds ratios (95% confidence interval) against sales workers as a reference (ref).

The lower row shows a *P*-value of <.01** or <.05* were considered to be statistically significant

The upper row shows odds ratios (95% confidence interval) against sales workers as a reference (ref).

[†]High activity group included agriculture, construction and mining, and carrying, cleaning and packing.

[‡]Low activity group included administrative and managerial, professional and clerical support.

late twentieth century onwards, and have coincided with the growth of the welfare state and the increasing urbanization of the population.

Another important change has been the increase in female labor in the workplace. Women have been released from a life of domestic servitude in the home and have become increasingly engaged in the workforce.

Such factors outlined above may have strongly influenced the occupational factors associated with national cancer incidence and mortality in Japan.

4.2 | Agriculture

Previous studies indicated that agricultural workers represent a unique population, possibly due to differences in lifestyle or their exposure to risky environmental hazards. Such workers deal with many potential hazards that include pesticides, chemical and biological agents, and the operation of heavy equipment. However, a lower prevalence of smoking plus high occupational activity has been reported[24,25] for this sector and this may have influenced the low mortality and morbidity rates from cancers observed among farmers.[25]

In a previous large Canadian cohort study linked with cancer registry records, hazard ratios of the agriculture sector for lung, colon, bladder, kidney and liver cancers were found to be significantly lower than for other occupational workers.[25] The risk reduction observed for kidney, bladder and colon cancers may be because of the working conditions of agricultural workers that involve high physical activity, a recognized modifiable risk factor for such cancers.[26] An analysis from a Spanish population-based case-control study revealed no significant association between male farmers and pancreatic cancer.[27] In comparison, for prostate cancer, established risk factors were age, ethnicity, and a positive family history of prostate cancer when comparing farmers to non-farmers.[28]

Farmers tend to not have an occupational retirement age since they are limited by physical strength and health, even though the normal time for retirement in Japan is between 60 and 65 years. In our study, although farmers were somewhat older than those employed in other occupations, the risk was significantly lower for all sites of cancer than that of other occupations. This difference explains how a risk-reductive process may exist in the agricultural sector.

In Japan in the middle of the twentieth century, about 18 million people were employed in agriculture, then one of the largest occupational groups. Since the economic significance of the agricultural sector has declined in parallel with an increase in the service sector, the proportion of people employed in this sector decreased to 6.3 million by the end of the last century.[29] Thus, the particular reasons for cancer risk reductions in agriculture must be understood against a background of a decline and graying of the farming population.

4.3 | High occupational physical activity and a paradox

In this study, we found significant associations between high levels of OPA and the risk of common cancers in males. This suggests that OPA may have some impact on the risk of developing cancer.

The present study is in agreement with previous studies reporting an association between high physical activity (including both occupational and leisure time) and cancer occurrence.[12-14] Although the mechanism is as yet undefined, both hormonal and nonhormonal causal relationships between physical activity and cancer are suspected.[26] An association between physical activity and hyperinsulinemia, inflammation, and immune disorders are potential nonhormonal etiologies of cancer.[30,31] In comparison, in an example of a hormonal factor involved in the development of cancer, it was shown that physical activity helped reduce levels of cancer-relevant biomarkers such as estradiol by preventing any above-normal weight gain.[32,33] Since, cancers are known to be obesity-related, it is unclear whether physical activity or obesity is the key to carcinogenesis.[26]

It has also been reported that only recreational physical but not occupational activity diminished the cancer risk.[16] The so-called "physical activity health paradox" may be due to the difference in characteristics of recreational and occupational physical activities.[34] This phenomenon has been mainly discussed in relation to cardiovascular disease,[17,35] but with regard to lung cancer, the same tendency has been reported.[16]

In this study, the physical activity health paradox was not observed since the high OPA group showed low rates of obesity and a low risk of cancer. One may speculate that the effect of a low percentage of obesity due to high OPA may cause a reduction in risk rather than being an unhealthy result due to a specific OPA. The interwoven complexity of physical activity, obesity, and cellular pathways in cancer is yet to be disentangled. However, it is plausible that sedentary behavior may contribute to carcinogenesis.

4.4 | Strengths and limitations

As far as we are aware, we are the first to investigate the association between occupations, especially OPA, and the risk of developing common cancers (not mortality) in Japan. This study is also one of the largest studies on the risk of developing cancer reported in the country. The particular strengths of this study include accurate diagnoses, which were directly extracted from medical charts in contrast to the less accurate diagnoses from claims data as done in other studies.[36] The exposure to a specific OPA was estimated, with quantification based on the amount of physical activity, measured with an accelerometer categorized more specifically by NHANES.[21]

However, despite this, several limitations may still exist. First, the content of ICOD-R may have been flawed. Other factors relevant to the study, such as the presence of pathogenic organisms (ie, *Helicobacter pylori* in stomach cancer, hepatitis virus in liver cancer) or socioeconomic status (ie, amount of income, educational attainment) could not be evaluated due to the limitations of the data. In addition, our data were not designed to detect occupational exposure to carcinogens or the high risks associated with specific occupational situations.[37] But, with regard to several established risk factors, low physical activity still remained a risk for several cancers.[12,14,38] Although our findings do not elucidate a specific relationship between OPA and cancer, the associations identified in this study may be implied.

Because ICOD-R is not a relevant population-based database, the hospital-based case-controls we used may have had a selection bias. In addition, one-third of the missing information within an occupation may amplify any selection bias even though all available factors were included as covariates in statistics. This problem arose because the return of occupational data from patients was not enforced because of concerns about the protection of patients' privacy. This has the effect of making any selection bias stronger and may have affected results that were insignificant for each occupational risk in females. An information bias existed in terms of misclassifications in occupational categories because data recall was from disease onset. Confirmation of this can be found in a previous study since occupational profiles in this database are nationally representative.[19] These are issues that need to be resolved in future in order to increase the accuracy of the dataset.

Second, a screening bias existed within the results. Though, medical checkup systems are widespread and covered on a national basis by medical insurance in Japan, disparities still exist in terms of opportunities for undergoing a medical examination among occupations and residential areas. Agriculture workers tend to work in self-owned businesses and live in rural areas, so that the chance of diagnosing carcinoma is likely lower than for other occupations. We could not adjust such an inequality in the chance to undergo screening even though adjustments for areas were undertaken.

Finally, evaluating occupational risk using the longest-held job may have led to a biased influence. The identified occupations used in this study were those in which individuals were mainly engaged in throughout their lifetime. On this point, this is a more accurate assessment of occupational risk than choosing the occupation of the patient at the time of death.[11,20] However, this may not always be the most relevant for deducing cancer risk. Considering the incubation time from exposure to an OPA adds to the risk of carcinogenicity, in any future studies using whole occupations over a lifetime and the time lag to developing cancer must be estimated.

More detailed studies in future will evaluate the occupational aspects of cancer causal relationships in an increasingly statistical manner.

5 | CONCLUSION

We have documented occupational inequalities in the risk of developing various cancers in Japanese workers. High levels of occupational physical activity are associated with a decreased risk of various cancers in men and decreased breast cancer in women. Further research on occupational physical activity and cancer risk in another large population may lead to an improvement in the health of the general population.

CONFLICTS OF INTEREST

None.

AUTHOR CONTRIBUTIONS

Rena Kaneko: Funding acquisition, conceptualization, resources, formal analysis, writing—original draft, review and editing. Masayoshi Zaitsu: Review and editing. Yuzuru Sato: Funding acquisition, review and editing. Yasuki Kobayashi: Funding acquisition, supervision, review and editing.

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.

INFORMED CONSENT

This study involved a retrospective analysis of data that had already been obtained through a national survey. As we did not use any personally identifiable information based on existing regulations in Japan, personal informed consent was not required.

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RESEARCH ARTICLE

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Sex-specific analysis of renal cell carcinoma histology and survival in Japan: A population-based study 2004 to 2016

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Abstract

Background and aims: In Western countries, sex differences in renal cell carcinoma (RCC) histology and survival have been previously described: compared with men, clear cell subtype is more common but overall prognosis is better among women. The goal of the present study was to examine sex differences in RCC histology and survival in Japan, using a large-scale population-based data set.

Methods: With the use of a population-based cancer registry in Japan (2004-2016), patients with primary RCC were followed for 5 years (median follow-up time 2.1 years). We distinguished histological subtypes of clear cell, papillary, and chromophobe from "others" subtype. Sex-specific prevalence ratio (PR) for each histological subtype was estimated by Poisson regression with robust variance, adjusted for age and year of diagnosis. Sex-specific survival rates were estimated by Cox proportional hazard regression, adjusted for age, year of diagnosis, histological subtypes, and other prognostic variables, with multiple imputation.

Results: The prevalence of clear cell and "others" subtypes was similar between men and women among all the 5265 study subjects during the 12 years of study (clear cell, male 88.6% vs female 87.1%; "others", male 5.3% vs female 5.3%). However, papillary subtype was less common among women than men (male 4.6% vs female 2.8%; PR = 0.63; 95% CI, 0.45-0.88), while chromophobe subtype was more common among women (male 1.6% vs female 4.8%; PR = 3.18; 95% CI, 2.26-4.47). Although "others" subtype (but not papillary/chromophobe subtypes) independently predicted prognosis (HR = 1.74; 95% CI, 1.32-2.30), no sex differences were observed in RCC survival.

Conclusion: We did not observe a statistically significant difference in the prevalence of clear cell subtype between men and women in Japan, which differs from the pattern previously described in Western countries. Sex differences in RCC histology may not affect RCC survival in this population.

KEYWORDS
kidney cancer, pathology, population-based, sex difference, survival

1 | INTRODUCTION

Renal cell carcinoma (RCC) ranks as the sixth most common type of cancer in men and 10th among women, worldwide, accounting for 5% and 3% of overall cancer incidence, respectively.[1] The incidence rate for RCC in Asian countries, including Japan, is roughly one-third compared with that in Western countries,[1] and the lower RCC incidence in Japan may be attributable to the lower prevalence of obesity (a prominent risk for RCC[2]) in that country compared with the Western settings. However, the incidence has been rising in recent years in Japan.[1-3] Advanced imaging modalities, together with changes in lifestyle and behavioral risks (such as smoking, obesity, hypertension, and occupational stress), may underlie the increase in incidence.[3-5]

Prognostic differences according to histological subtypes are well described. In the United States (USA), studies using the Surveillance, Epidemiology, and End Results (SEER) database suggest that the most common histological subtype is the clear cell subtype (approximately 80%-90%), followed by the papillary (approximately 4%-13%) and chromophobe (approximately 2%-5%) subtypes.[6-8] Compared with the clear cell subtype, patients with papillary and chromophobe subtypes tend to have better prognosis (hazard ratio [HR] approximately 0.67-0.98), but patients with other rare histological subtypes (eg, collecting duct and sarcomatoid differentiation) tend to have a poorer prognosis (HR approximately 1.81-2.21).[8] Previous single-center studies in the United States are consistent with this pattern.[9,10]

More recently, studies in Western settings have reported sex differences in RCC histology and survival.[11-14] The clear cell subtype is likely more prevalent among women compared with men (88% vs 85%).[11] In addition, among all incident RCC, the papillary subtype tends to be approximately 0.5 to 0.6 times less prevalent, but the chromophobe subtype tends to be approximately 1.6 to 2.3 times more prevalent among women compared with men.[12,13] Sex differences in RCC histology, particularly in the clear cell subtype, may be partly attributed to lifestyle and behavioral factors such as obesity,[15] which is generally more prevalent in women than men across most countries,[16] and smoking.[17] However, compared with men, RCC prognosis has been reported to be better among women (HR 0.92) even though the clear cell subtype, which has a more unfavorable prognosis, was more prevalent among women.[11] Other female clinicopathological features (lower pathological grade, earlier stage of detection, and higher prevalence of chromophobe subtype) linked to favorable prognosis may underlie these paradoxical sex differences in RCC histology and survival.[8,11-13]

Reports of sex differences in RCC histology and survival remain scarce in Asian settings. For example, in Japan, although the Japanese Urological Association has reported descriptive statistics of RCC histology and 5-year overall survival with multicenter data (but not population-based data),[18] sex differences in RCC histology and survival have not been previously assessed. One study in South Korea, with 1508 RCC patients, examined sex differences and reported lower prevalence of clear cell subtypes among women compared with men (female 72% vs male 84%) but a nonsignificant sex difference in survival, which contradicts the Western pattern.[19] However, this was a relatively small, single-center study, and it was not population based.

Accordingly, the goal of the present study was to examine sex differences in RCC histology and survival in Japan, using a large-scale population-based data set with over 5000 RCC patients. We sought to examine whether sex differences exist in RCC histology and whether there are overall survival differences by sex and by histological subtypes in Japan. Also, we sought to determine whether a sex difference in survival, if there is one, persists even after controlling for histological subtypes and other potential prognostic factors such as pathological grade, tumor stage, treatment, socioeconomic status (SES), and smoking habits.

2 | MATERIALS AND METHODS

2.1 | Data setting and study subjects

A large, population-based data set (2004-2016) of Kanagawa Cancer Registry (KCR), a survey of over nine million people in Kanagawa prefecture that covers approximately 7% of the Japanese population, was used for analysis. Details of the study database have been previously described elsewhere.[20,21] Briefly, Kanagawa Prefecture, a metropolitan prefecture located next to Tokyo, is the second largest prefecture in Japan, and KCR is one of the largest local cancer registries in Japan. Well-trained tumor registrars certified by the training program of the Japanese Association of Cancer Registries, whose program is accredited by SEER, are responsible for data collection. The data included basic information (sex, age, date of diagnosis, and date of death/last follow-up) and clinical information (pathology, stage, and treatment). Uniquely, KCR collected information on occupation and smoking behaviors, if available, during the study period (approximately 10% of the registered cases); however, these data are no longer obtained since 2016 because of a change of data management practice. KCR automatically updates dates of death/last follow-up with population registers and death certificates, and previous diagnosis codes, as well as pathological codes, are updated to be consistent with changes in coding practice. We obtained a deidentified data set under the research agreement between the authors and KCR, and the research ethics committee of The University of Tokyo, Tokyo (Protocol Number 3891-4), approved the study.

We included all 7525 RCC patients registered in the KCR (a) who were diagnosed with RCC (C64 in International Classification of Diseases, 10th revision) between 2004 and 2014, (b) aged 20 and above, and (c) who had complete observation duration. We excluded those who had missing data for pathological type.

2.2 | Histological subtype and 5-year overall survival

Using pathology codes (identified by International Classification of Disease for Oncology, Third edition [ICD-O-3] pathology codes), we distinguished the histological subtypes of clear cell (ICD-O-3 codes of 8310, 8312, 8316, and 8320), papillary (ICD-O-3 code of 8260), and chromophobe (ICD-O-3 codes of 8270 and 8317) from "others" subtype (eg, collecting duct and sarcomatoid differentiation), according to previous SEER studies.[6,8,22]

The 5-year overall survival was defined by the right-censored, observation duration (person-years) from the date of initial diagnosis to the date of death/last follow-up (median follow-up time, 2.1 years).

2.3 | Covariates

The age (1-year age category) and year of diagnosis (calendar year) were adjusted as continuous variables across all statistical models. To control for secular changes in clinicopathological diagnosis and treatment regimens, including surgery and systemic therapies, over time,

TABLE 1 Characteristics of renal cell carcinoma patients in Kanagawa Cancer Registry

	Mean (SD) or Number (%)[a]						
	Crude				Multiple Imputation[c]		
Characteristics	All n = 5265	Men n = 3820	Women n = 1445	*P*[b]	All n = 5265	Men n = 3820	Women n = 1445
Basic characteristics							
Histology[d]							
Clear cell	4642 (88.2%)	3383 (88.6%)	1259 (87.1%)	.15	88.2%	88.6%	87.1%
Papillary	217 (4.1%)	176 (4.6%)	41 (2.8%)	.004	4.1%	4.6%	2.8%
Chromophobe	129 (2.5%)	60 (1.6%)	69 (4.8%)	<.001	2.5%	1.6%	4.8%
Others	277 (5.3%)	201 (5.3%)	76 (5.3%)	>.99	5.3%	5.3%	5.3%
Age, y	64 (12)	64 (12)	65 (12)	<.001	64 (12)	64 (12)	65 (12)
Year of diagnosis	2009 (3)	2009 (3)	2009 (3)	.23	2009 (3)	2009 (3)	2009 (3)
Other backgrounds[e]							
Pathological grade	n = 3,368	n = 2,424	n = 944				
High grade	355 (10.5%)	257 (10.6%)	98 (10.4%)	.85	12.6%	12.5%	12.7%
Stage	n = 3791	n = 2753	n = 1038				
Late stage	983 (25.9%)	724 (26.3%)	259 (25.0%)	.40	32.9%	33.1%	32.3%
Treatment	n = 4922	n = 3562	n = 1360				
Surgery	4656 (94.6%)	3368 (94.6%)	1288 (94.7%)	.83	94.2%	94.1%	94.2%
SES	n = 359	n = 316	n = 43				
High-SES	73 (20.3%)	62 (19.6%)	11 (25.6%)	.36	27.5%	27.7%	27.1%
Smoking	n = 1603	n = 1162	n = 441				
Ever smoker	789 (49.2%)	712 (61.3%)	77 (17.5%)	<.001	49.6%	61.8%	17.4%
5-y overall survival, %							
Overall	72.0%	72.0%	71.9%	.95	72.0%	72.0%	71.9%
Clear cell	74.2%	74.0%	74.8%	.61	74.2%	74.0%	74.8%
Papillary	75.4%	76.7%	70.1%	.45	75.4%	76.7%	70.1%
Chromophobe	89.0%	91.8%	86.1%	.48	89.0%	91.8%	86.1%
Others	30.3%	33.3%	22.6%	.06	30.3%	33.3%	22.6%

Abbreviation: SES, socioeconomic status.

[a]Percentage may not total 100 because of rounding and multiple imputation.

[b]*P* values are for chi-squared test or *t* test.

[c]Data were estimated with 20 imputed data sets. The number of missing data was, respectively, as follows: pathological grade (1897, 36.0%), stage (1474, 28.0%), surgery (343, 6.5%), SES (4906, 93.2%), and smoking habits (3662, 69.6%).

[d]The distribution of all histological subtypes combined differed between men and women (chi-squared test, $P < .001$).

[e]Missing data are included.

we adjusted for year of diagnosis. Additionally, clinicopathological variables were included in survival analyses as potential mediating variables, ie, these variables do not confound the association between sex and RCC survival, but rather, they may help to explain the observed differences. Our clinicopathological variables of interest included the following[3-6,17,20-22]: WHO pathological grade (grades 3 or 4 [high-grade] vs grades 1 or 2 [low-grade]), the Union for International Cancer Control TNM stage (stages III and IV [late stage] vs stages I and II [early stage]), and any performed surgeries including radical/partial nephrectomy (yes/no), as well as SES (high SES [with the longest-held occupational class of managerial or professional workers] vs low SES) and smoking habits (never/ever).

2.4 | Statistical analysis

The background characteristics between men and women were compared by *t* test or chi-squared test. The 5-year overall survival rates were estimated with Kaplan-Meier curves and compared by log-rank test. Except for basic characteristics (age, sex, year of diagnosis, and survival time) and histological subtypes, records included missing data on mediating factors: pathological grade (1897, 36.0%), stage (1474, 28.0%), surgery (343, 6.5%), SES (4906, 93.2%), and smoking habits (3662, 69.6%). Excluding patients with missing data may lead to biased inference; therefore, we conducted multiple imputation for missing data among the 5265 study subjects with all variables used for analysis, and 20 imputed data sets were generated by the Multiple Imputation by Chained Equations method (Table 1).[3-5,23]

In our main analytic model for the sex difference in histology (model 1), prevalence ratio (PR) and 95% confidence interval (CI) for each histological subtype were estimated by Poisson regression with robust variance, adjusted for age and year of diagnosis.[23] Male patients served as the reference group for all analyses. In a Poisson regression with multiple imputation, we further controlled for pathological grade and stage (model 2) and SES and smoking habits (model 3) as potential mediating variables. In prior analyses, according to the methodology used in previous studies (multinomial logistic regression model),[3,9] we estimated multinomial odds ratios (in other word, relative risk ratios) for each type of RCC against clear cell subtypes among women compared with men. The magnitude and direction of odds ratios for each histological subtype were almost the same to the PRs for each histological subtype. However, we chose PRs for the final analytic method because the "prevalence" of each type of RCC among all primary RCC would be more intuitively rational compared with "odds" of each type of RCC against a specific RCC (ie, clear cell).

For sex differences in the RCC survival, HRs and 95% CIs for overall death were estimated by Cox proportional hazard model, adjusted for age and year of diagnosis (model 1). Male patients served as the reference group for all analyses. In a Cox regression with multiple imputation, we further controlled for histological subtypes (model 2) and pathological grade and stage (model 3) as potential mediating variables. Finally, in the maximally adjusted model, we controlled for all potential covariates (histological subtypes, pathological grade, stage, surgery, SES, and smoking habits, model 4).

In sensitivity analyses, because of the potential background differences between those who completed histological subtypes and those who did not complete histological subtypes, we performed regression analyses among all 7525 RCC patients (including 2260 patients who did not have complete histological information) with multiple imputation. Additionally, complete case analyses were performed. In the complete case analysis, SES was excluded from covariates because of the small sample size for the complete data. Alpha was set at .05, and all *P* values were two sided. Data were analyzed using STATA/MP13.1 (StataCorp LP, College Station, Texas).

3 | RESULTS

From all 7525 RCC patients registered in the KCR who were aged 20 years and above (mean age [SD], 66 [13] y), we excluded those with missing data on pathological type (2260 patients, 30.0%), leaving a retrospective cohort comprising 5265 RCC patients (male 3820 [72.6%], female 1445 [27.4%]) for analysis. The percentage of missing data for pathology differed between men and women (male 28.8%, female 33.0%, $P < 0.001$, chi-squared test). Among all 7525 RCC patients, the percentages of microscopic verification and Death Certificate Only were 70.0% and 11.9%, respectively.

For histological subtypes, the distribution differed between men and women (Table 1). The prevalence of clear cell and "others" subtype was similar between men and women (clear cell, male 88.6%, female 87.1%; "others," male 5.3%, female 5.3%). However, the papillary subtype was less prevalent among women compared with men (male 4.6%, female 2.8%, $P = .004$, chi-squared test), while chromophobe subtype was more prevalent among women compared with men (male 1.6%, female 4.8%, $P < 0.001$, chi-squared test; Table 1). Except for histological subtypes, age, and smoking habits, background characteristics and 5-year overall survivals did not show a statistically significant difference between men and women (Table 1).

In Poisson regression with robust variance, although the maximally adjusted PR of clear cell subtype showed a marginally lower prevalence in women (PR = 0.97, 95% CI, 0.96-0.996, model 3), the PRs of clear cell subtype in model 1 and model 2 did not significantly differ between men and women (Table 2). Papillary subtype was less prevalent in women compared with men (model 1, Table 2): PR = 0.63 (95% CI, 0.45-0.88). By contrast, chromophobe subtype was more prevalent in women (PR = 3.18; 95% CI, 2.26-4.47). Even in the maximally adjusted model, papillary subtypes remained less prevalent, but chromophobe subtypes remained more prevalent in women compared with men (model 3, Table 2). The PR of the "others" subtype did not differ between men and women (Table 2).

In survival analyses, although the 5-year overall survival rate was 72% in this population, patients with the "others" subtype had a poor prognosis (30.3%, Table 1). However, no statistically significant differences were observed between men and women, even after stratifying by histological subtypes (Table 1). In the Cox regression analysis,

TABLE 2 Prevalence ratios for each histological subtype estimated by Poisson regression with robust variance

	Prevalence Ratio (95% Confidence Interval), n = 5265					
Characteristics	**Model 1**	***P***	**Model 2[a]**	***P***	**Model 3[a]**	***P***
Clear cell						
Women	0.98 (0.96, 1.01)	.15	0.98 (0.96, 1.01)	.13	0.97 (0.94, 1.00)	.03
Age, continuous	1.00 (1.00, 1.00)	.63	1.00 (1.00, 1.00)	.78	1.00 (1.00, 1.00)	.92
Year of diagnosis, continuous	0.99 (0.99, 0.99)	<.001	0.99 (0.99, 0.99)	<.001	0.99 (0.99, 0.99)	<.001
High grade			0.74 (0.69, 0.80)	<.001	0.74 (0.69, 0.80)	<.001
Late stage			0.98 (0.94, 1.02)	.35	0.98 (0.95, 1.02)	.42
High SES					1.00 (0.94, 1.07)	.98
Ever smoker					0.97 (0.93, 1.01)	.11
Papillary						
Women	0.63 (0.45, 0.88)	.007	0.62 (0.44, 0.87)	.006	0.67 (0.46, 0.98)	.04
Age, continuous	1.00 (0.99, 1.01)	.90	1.00 (0.99, 1.01)	.97	1.00 (0.99, 1.01)	.98
Year of diagnosis, continuous	1.18 (1.12, 1.23)	<.001	1.16 (1.10, 1.22)	<.001	1.16 (1.10, 1.22)	<.001
High grade			2.04 (1.38, 3.03)	<.001	2.03 (1.36, 3.02)	<.001
Late stage			0.65 (0.45, 0.95)	.03	0.64 (0.44, 0.94)	.02
High SES					0.98 (0.63, 1.52)	.91
Ever smoker					1.19 (0.83, 1.72)	.34
Chromophobe						
Women	3.18 (2.26, 4.47)	<.001	3.14 (2.23, 4.42)	<.001	3.30 (2.23, 4.87)	<.001
Age, continuous	0.98 (0.97, 1.00)	.009	0.98 (0.97, 1.00)	.02	0.98 (0.97, 1.00)	.03
Year of diagnosis, continuous	1.18 (1.11, 1.27)	<.001	1.16 (1.08, 1.25)	<.001	1.16 (1.07, 1.24)	<.001
High grade			1.35 (0.71, 2.55)	.36	1.36 (0.73, 2.55)	.34
Late stage			0.39 (0.21, 0.74)	.004	0.39 (0.21, 0.72)	.003
High SES					1.03 (0.48, 2.23)	.93
Ever smoker					1.11 (0.69, 1.81)	.66
Others						
Women	0.97 (0.75, 1.26)	.84	0.99 (0.78, 1.27)	.96	1.18 (0.83, 1.67)	.35
Age, continuous	1.02 (1.00, 1.03)	.01	1.01 (1.00, 1.02)	.20	1.01 (1.00, 1.02)	.16
Year of diagnosis, continuous	0.99 (0.95, 1.03)	.59	1.00 (0.96, 1.04)	.96	1.00 (0.95, 1.04)	.94
High grade			6.21 (4.04, 9.53)	<.001	6.21 (4.06, 9.50)	<.001
Late stage			2.55 (1.38, 4.73)	.004	2.47 (1.35, 4.51)	.004
High SES					0.95 (0.43, 2.13)	.90
Ever smoker					1.47 (0.86, 2.51)	.15

Abbreviation: SES, socioeconomic status.
[a]Data were estimated with 20 imputed data sets.

although the chromophobe subtype predicted a better prognosis and the "others" subtype predicted a poor prognosis, only the "others" subtype predicted prognosis in the maximally adjusted model (HR 1.74; 95% CI 1.32-2.30, model 4, Table 3). However, we did not observe a statistically significant difference in the 5-year overall survival between men and women in model 1 through model 4 (Table 3).

In sensitivity analyses, the observed patterns were almost identical to the main results (Table 4). The multinomial odds ratios of women for the papillary, chromophobe, and "others" subtypes were, respectively, 0.64 (95% CI, 0.45-0.91), 3.25 (95% CI, 2.28-4.64), and 0.99 (95% CI, 0.75-1.30).

4 | DISCUSSION

As far as we are aware, this is the first analysis of sex differences in histology and survival in RCC patients in Japan. Compared with men, although women did not have a significantly different prevalence for clear cell and "others" subtypes, women had different prevalence for papillary and chromophobe subtypes (0.6 times lower prevalence for papillary subtype and 3.2 times higher prevalence for chromophobe subtype). Even after controlling for potential mediating factors, the sex difference for these histological subtypes persisted. However, the survival was similar between men and women, even after accounting

TABLE 3 Hazard ratios for 5-year overall survival estimated by Cox proportional hazard model

	Hazard Ratio (95% Confidence Interval), n = 5265							
Characteristics	**Model 1**	***P***	**Model 2**	***P***	**Model 3[1]**	***P***	**Model 4[1]**	***P***
Women	0.95 (0.82, 1.08)	.42	0.99 (0.86, 1.13)	.88	0.98 (0.84, 1.15)	.84	1.13 (0.94, 1.37)	.20
Age	1.04 (1.03, 1.04)	<.001	1.03 (1.03, 1.04)	<.001	1.03 (1.02, 1.04)	<.001	1.03 (1.02, 1.03)	<.001
Year of diagnosis	1.07 (1.04, 1.10)	<.001	1.08 (1.05, 1.10)	<.001	1.11 (1.07, 1.16)	<.001	1.13 (1.08, 1.17)	<.001
Histological subtypes								
Clear cell			1.00		1.00		1.00	
Papillary			0.84 (0.59, 1.19)	.32	0.84 (0.59, 1.20)	.34	0.89 (0.62, 1.28)	.53
Chromophobe			0.38 (0.19, 0.76)	.006	0.47 (0.23, 0.98)	.04	0.51 (0.25, 1.06)	.07
Others			4.69 (3.97, 5.53)	<.001	2.15 (1.64, 2.83)	<.001	1.74 (1.32, 2.30)	<.001
High grade					2.52 (2.03, 3.13)	<.001	2.43 (1.95, 3.03)	<.001
Late stage					4.30 (3.33, 5.54)	<.001	3.62 (2.77, 4.74)	<.001
Any surgery							0.27 (0.21, 0.35)	<.001
High SES							1.16 (0.74, 1.83)	.51
Ever smoker							1.26 (0.94, 1.70)	.12

Abbreviation: SES, socioeconomic status.
[1]Data were estimated with 20 imputed data sets.

for survival differences by histological subtypes (eg, RCC patients with "others" subtype had 1.7 times poorer survival), as well as other potential prognostic factors.

Differences in female lifestyle and behavioral risks (obesity and smoking) between Western countries and Japan may underlie our observed sex difference in RCC histology of the clear cell subtype,[15,17] which differs from the pattern seen in Western countries.[8,13,22] Although the prevalence of the clear cell subtype varies across populations and regions, studies in the United States and Europe consistently suggest a higher prevalence of the clear cell subtype among women, by approximately 2% to 7%.[8,11-14,22] However, the prevalence of the clear cell subtype was not higher among women compared with men in our study population in Japan, which partly coincides with the result from South Korea.[19] Studies imply potential pathways of group-based differences in the risk for the clear cell subtype via obesity, smoking, hypertension, and end-stage renal disease in combination with genetic factors (APOL1 gene).[1,12,13,15,17,24] Since obesity and smoking habits are far less common among Asian women compared with their counterparts in Western countries,[16,25] the flat "gradient" of sex difference in the clear cell subtype seems plausible as an explanation for the discrepancy between the results obtained from Western and Asian countries.

TABLE 4 Sensitivity analyses for sex differences in renal cell carcinoma histology and survival by Poisson regression with robust variance and Cox proportional hazard model

Prevalence Ratio (95% Confidence Interval)	**All Patients (n = 7525)[a]**	***P***	**Complete Case (n = 790)[b]**	***P***
Clear cell				
Women	0.97 (0.94, 1.01)	.12	0.97 (0.92, 1.02)	.29
Papillary				
Women	0.67 (0.46, 0.99)	.04	0.74 (0.31, 1.74)	.48
Chromophobe				
Women	3.12 (2.01, 4.87)	<.001	3.46 (1.49, 8.00)	.004
Others				
Women	1.07 (0.84, 1.37)	.57	1.19 (0.33, 4.35)	.79
Hazard ratio (95% confidence interval)	**All patients (n = 7525)[c]**	***P***	**Complete case (n = 787)[d]**	***P***
Women	1.11 (0.99, 1.24)	.08	1.30 (0.74, 2.25)	.36

[a]Data were estimated with 20 imputed data sets. The numbers of missing data were, respectively, as follows: histological subtypes (2260, 30%), pathological grade (4156, 55%), stage (3296, 44%), surgery (1481, 20%), socioeconomic status (7113, 94%), and smoking habits (5569, 74%). Adjusted for age, year of diagnosis, pathological grade, stage, socioeconomic status, and smoking habits.
[b]Adjusted for age, year of diagnosis, pathological grade, stage, and smoking habits.
[c]Data were estimated with 20 imputed data sets. Adjusted for age, year of diagnosis, histological subtype, pathological grade, stage, treatment, socioeconomic status, and smoking habits.
[d]Adjusted for age, year of diagnosis, histological subtype, pathological grade, stage, treatment, and smoking habits.

The sex difference in the other RCC histological subtypes may be consistent with the data from Western countries. In the Western settings, previous studies suggested that the papillary subtype was less prevalent (OR approximately 0.5 to 0.6) but that the chromophobe subtype was more prevalent (OR 2.3) among women compared with men.[12,13] In our population-based study in Japan, we confirmed this pattern with similar magnitudes and directions (PRs for papillary and chromophobe subtypes were, respectively, 0.63 and 3.18). Some biological mechanisms, eg, androgen receptor expression,[26] may play a role. Yet, this sex difference is not well-characterized via biological pathways. In addition, the prevalence of the papillary (4.1%) and chromophobe (2.5%) subtypes in the total analyzed population, which parallels the statistics of the Japanese Urological Association,[18] is likely at the lower end of published estimates compared with data from previous studies,[6-8,12,13,19] suggesting regional disparity in RCC histology.

Regarding sex disparities in RCC survival, women have been previously reported to have better prognosis compared with men,[11,14,19] which we did not observe in the present study. In the Western settings, better prognostic factors, including smaller tumor size, low pathological grade, and early stage, are likely more prevalent among women compared with men.[11,14,27] However, in this non-Western setting, we did not observe a sex difference in grade/stage. Similarly, a sex difference for grade/stage/tumor size was not found in South Korea.[19] The similar distributions of better prognostic factors between men and women might partly underlie the observed absence of sex disparity in RCC survival in our study, as opposed to studies in the Western setting.[11]

Several limitations in this study should be noted. First, although our data set was population-based, it only represents approximately 7% of the Japanese population in one geographic region, and our obtained pathology diagnoses were not based on a central pathology review. In addition, other relevant outcomes (eg, relative survival)[28] were not evaluated, and complete data were limited for histology and other prognostic variables (including stage) because of missing data, thereby limiting internal and external generalizability. However, our sensitivity analyses with multiple imputation and complete data yielded almost identical results. Second, although we assessed SES and smoking habits, we could not assess other potential predicting factors such as metabolic disorders (eg, obesity, hypertension, and diabetes), tumor size, or performance status, as seen in previous studies.[1,6,10,11,19] However, hypertension and diabetes did not affect prognosis in a previous study in South Korea.[19] Third, because of the limitation of the data, we were not able to classify histological subtypes further (such as type 1 and type 2 papillary RCC).[28] Since patients with type 2 papillary RCC tend to have poorer prognosis,[29] future studies focusing on sex differences in papillary RCC subtypes are needed.

Despite these limitations, the strengths of our study included the size, as this is one of the most extensive studies conducted for evaluating sex differences in RCC histology in the non-Western setting. Our distribution of the clear cell subtype (88.2%) estimated with population-based data was similar to the SEER data,[6,7,11,21] suggesting our reduced bias compared with nonpopulation-based studies.[18,19] In addition, while previous population-based studies did not include SES or smoking habits,[11] we were able to take account of these characteristics in our study.

Lastly, RCC patients with the "others" subtype tend to have a poorer prognosis compared with those with the clear cell subtype,[8,30] and we confirmed this disparity in Japan. In contrast to good prognoses in clear cell, papillary, and chromophobe subtypes (even though survivals tend to differ slightly among the three subtypes),[7] prognosis of the "others" subtype remains poor, with aggressive pathological features (eg, approximately 50% of RCC patients having the "others" subtype tend to present with metastasis).[8] Hence, further studies exploring effects of standard and novel agents for this high-risk population are warranted.[29]

In conclusion, sex differences in RCC histology (papillary and chromophobe subtypes but not clear cell and other subtypes) appear to exist in Japan, which differs from the pattern previously described in Western countries. Sex differences in RCC histology may not affect RCC survival in this population. Further understanding of RCC etiology from an integrated perspective of social and clinicopathological epidemiology may elucidate the determinants of sex differences in RCC histology and prognosis.

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CONFLICT OF INTEREST

The authors declare no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

Conceptualization: Masayoshi Zaitsu, Ichiro Kawachi

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All authors have read and approved the final version of the manuscript. Masayoshi Zaitsu had full access to all of the data in this study and takes complete responsibility for the integrity of the data and the accuracy of the data analysis.

TRANSPARENCY STATEMENT

Masayoshi Zaitsu affirms that this manuscript is an honest, accurate, and transparent account of the study being reported, that no important aspects of the study have been omitted, and that any

discrepancies from the study as planned (and, if relevant, registered) have been explained.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the Kanagawa Cancer Registry. Restrictions apply to the availability of these data, which were used under license for this study by the Kanagawa Cancer Registry; research data used in the study cannot be made publicly available directly by the authors. If any person wishes to verify our data analysis, they are most welcome to contact the corresponding author.

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Original Article

Light to Moderate Amount of Lifetime Alcohol Consumption and Risk of Cancer in Japan

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BACKGROUND: Even light to moderate alcohol consumption has been shown to increase cancer incidence. However, this association has not been well characterized in Japan. **METHODS:** Based on a nationwide, hospital-based data set (2005-2016), a multicenter case-control study was conducted (63,232 cancer cases and 63,232 controls matched for sex, age, admission date, and admitting hospital). The total amount of lifetime alcohol consumption (drink-years) was recalled for each patient by multiplication of the daily amount of standardized alcohol use (drinks per day) and the duration of drinking (years). Odds ratios (ORs) were estimated for overall and specific cancer sites via conditional logistic regression with restricted cubic splines, with adjustments made for smoking, occupational class, and comorbidities. Lifetime abstainers served as the reference group. **RESULTS:** Spline curves showed a dose-response association with overall cancer risk: the minimum risk was at 0 drink-years, and the OR at 10 drink-years was 1.05 (95% confidence interval [CI], 1.04-1.06). In comparison with lifetime abstainers, the OR for >0 to 20 drink-years was 1.06 (95% CI, 1.01-1.11). Those who drank 2 drinks or fewer per day had elevated odds for overall cancer risk across all duration-of-drinking categories. The same patterns were observed at light to moderate levels of drinking for most gastrointestinal/aerodigestive cancers as well as breast and prostate cancers. Analyses stratified by sex, different drinking/smoking behaviors, and occupational class mostly showed the same patterns for overall cancer incidence associated with light to moderate levels of drinking. **CONCLUSIONS:** In Japan, even light to moderate alcohol consumption appears to be associated with elevated cancer risks. ***Cancer* 2020;126:1031-1040**.

KEYWORDS: alcohol, cancer incidence, Japan, lifetime, risk, smoking.

INTRODUCTION

Drinking alcohol is a contributor to the overall cancer burden. In Western settings, alcohol-related cancer risk has been characterized as a J-shape pattern in some instances (colorectal and kidney cancers), and this suggests potential protective effects of alcohol.[1-3] However, in 2018, the American Society of Clinical Oncology stated that more than 5% of new cancer cases were attributable to alcohol consumption.[4] Upper aerodigestive tract (oral, laryngeal, and esophageal), colorectal, and liver cancers represented 60%, 21%, and 13% of alcohol-related cancer cases in men, respectively, whereas breast, upper aerodigestive tract, liver, and colorectal cancers represented 52%, 25%, 12%, and 6% of alcohol-related cancer cases in women, respectively.[5] On the whole, upper aerodigestive cancers represent approximately 50% of the total cases, and they are followed by colorectal (16%), breast (16%), and liver cancers (13%).[5]

Recent studies have raised concerns about the risk of even light to moderate levels of alcohol consumption for cancer incidence.[6-8] In Japan as well as East Asian countries, previous studies regarding alcohol-related cancer risk are widely available for various cancer sites.[9-12] For example, in the Japan Public Health Center (JPHC)–based prospective study, the potential risk of light to moderate levels of alcohol consumption was implied to some extent with the use of trend analysis.[9,10] However, few studies have specifically focused on the cancer risk associated with light to moderate levels of alcohol consumption for overall cancer and specific cancer sites in Japan. Light to moderate levels of alcohol consumption may affect cancer risk through multiple pathways. For example, alcohol use increases circulating sex hormone levels, and this contributes to excess breast cancer risk.[13] In addition, acetaldehyde, a metabolite of ethanol classified as a group 1 carcinogen by the International Agency for Research on Cancer, stimulates

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[Correction added on 20 December 2019, after first online publication: Table 1 and the legend for Figure 3 have been updated.]

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cell proliferation and induces DNA damage.[6-10,13,14] The Japanese have a higher prevalence of polymorphisms in the aldehyde dehydrogenase 2 (ALDH2) enzyme, which makes them slower at metabolizing acetaldehyde.[9,14] Previous studies have indeed suggested an elevated cancer risk from alcohol consumption in the urinary tract and prostate in Japan, which has not been found in Western countries.[9,10,15-19] We have hypothesized that there may be an elevated cancer risk at even light to moderate levels of alcohol consumption in Japan due to a higher prevalence of ALDH2 polymorphisms in the Japanese.

Previous studies have elucidated the association between lifetime drinking behaviors and cancer risk by drinking frequency (eg, standard drinks per day)[2,13,20] and have used the weighted, averaged frequency of drinks over time. This frequency measurement would be relevant for capturing precise drinking behavior. Meanwhile, a less accurate but simple measurement of the lifetime carcinogen burden from drinking—the total amount of lifetime alcohol consumption (called *drink-years* hereafter) estimated by multiplication of the average daily amount of standardized alcohol units (drinks per day) and the duration of drinking (years)—has also been used in clinical settings, particularly for upper aerodigestive cancers.[21-24] Yet, the cancer risk associated with light to moderate drink-year levels has not been well characterized in Japan.

Accordingly, the goal of the current study was to investigate the cancer risk associated with light to moderate levels for the total amount of lifetime alcohol consumption. Using a nationwide, multicenter inpatient data set in Japan that contained clinical, behavioral (smoking and drinking), and occupational information,[16,17,25-28] we sought to examine whether light to moderate drink-year levels were associated with an elevated cancer risk after adjustments for smoking and occupational class disparities. In addition, we sought to determine whether the observed association persisted 1) even after we had fully controlled for alcohol-related lifestyle comorbidities (eg, hypertension, diabetes, and obesity); 2) within sex strata and with different drinking habits, drinking durations, and occupational classes; and 3) when the analysis was restricted to never smokers.[17,27,29]

MATERIALS AND METHODS

Study Setting

A nationwide, multicentered, hospital-based, matched case-control study was conducted with the Inpatient Clinico-Occupational Database of Rosai Hospital Group (ICOD-R), which is administered by the Japan Organization of Occupational Health and Safety. Details of the ICOD-R have been described elsewhere.[16,17,25-28] Briefly, the Rosai Hospital Group consists of 33 general hospitals throughout Japan. The ICOD-R includes medical chart information confirmed by physicians (eg, basic sociodemographic characteristics, pathological information, clinical history, and diagnosis of current and past diseases), the occupational history (current job and 3 most recent jobs with their duration), and the smoking and alcohol habits (status, daily amount, and duration) of every inpatient. Since 2005, it has also collected self-reported lifestyle-related comorbidities diagnosed at annual health check-ups (eg, hypertension, diabetes, and obesity).[17,27] The clinical diagnosis is coded according to *International Classification of Diseases, Ninth Revision* (*ICD-9*), or *International Classification of Diseases, Tenth Revision* (*ICD-10*), and the profiles of the patients are nationally representative. The ICOD-R is unique to the Rosai Hospital Group and so differs from medical claims data, which may have less diagnostic accuracy. Written informed consent is obtained, and trained registrars and nurses are responsible for registering the data. The database currently contains details from more than 6 million inpatients. We obtained a deidentified data set under the research agreement, and the local research ethics committees approved the study.

Cases and Controls

The study subjects included 126,464 individuals (63,232 cancer cases and their 63,232 hospital controls) aged 20 years or older who had been admitted to the hospital between 2005 and 2016. The cancer cases included those patients whose main diagnosis was an initial cancer (*ICD-9*, 140-208; *ICD-10*, C00-C97), as confirmed by physicians on discharge. Each cancer case had a diagnosis with a specific cancer site (Table 1). We defined cancer incidence as the first-time admission among patients who did not have a previous history of cancer, and the validation for the diagnosis has been described elsewhere.[16,17,25-28]

According to the methodology used in previous studies, our controls included patients diagnosed with eye and ear disease (360-389 [*ICD-9*] and H00-H95 [*ICD-10*]; 45.4%), genitourinary system disease (580-629 [*ICD-9*] and N00-N99 [*ICD-10*]; 38.3%), infectious and parasitic diseases (1-136 [*ICD-9*] and A00-B99 [*ICD-10*]; 10.6%), or skin diseases (680-709 [*ICD-9*] and L00-L99 [*ICD-10*]; 5.7%).[16,17,25-28] To select cases and controls from the same source population, we randomly sampled 1 control for each cancer case who was matched by the basic background characteristics of sex (male or female),

TABLE 1. Odds Ratios Estimated With the Continuous Total Amount of Lifetime Alcohol Consumption With Restricted Cubic Spline Methods

Primary Site	*ICD-10*	No. of Cases (%)	Age, Mean (SD), y	Women, %	Odds Ratio (95% CI) at 10 Drink-y Point	
					Model 1[a]	Model 2[b]
All sites	C00-C97	63,232 (100)[c]	69 (10)	34.7	1.05 (1.04-1.06)	1.05 (1.04-1.06)
Specific sites						
Lip, oral cavity, and pharynx	C00-C14	1045 (1.7)	67 (11)	25.6	1.10 (1.01-1.19)	1.09 (1.00-1.17)
Esophagus	C15	1408 (2.2)	69 (9)	13.1	1.45 (1.34-1.58)	1.44 (1.33-1.57)
Stomach	C16	9355 (14.8)	70 (10)	26.2	1.06 (1.03-1.09)	1.06 (1.04-1.09)
Colon and rectum	C18-C20	9637 (15.2)	69 (10)	38.3	1.08 (1.05-1.11)	1.08 (1.05-1.11)
Liver	C22	3604 (5.7)	70 (9)	27.8	1.03 (0.99-1.07)	1.03 (0.99-1.08)
Gallbladder and bile duct	C23, C24	1350 (2.1)	73 (9)	42.7	1.04 (0.97-1.11)	1.04 (0.97-1.11)
Pancreas	C25	1496 (2.4)	71 (9)	42.7	1.02 (0.95-1.09)	1.03 (0.96-1.10)
Larynx	C32	549 (0.9)	69 (9)	5.1	1.22 (1.08-1.37)	1.23 (1.09-1.38)
Lung	C33, C34	5972 (9.4)	71 (9)	27.1	0.97 (0.94-1.00)	0.97 (0.93-1.01)
Bone and soft tissue	C40, C41, C46-C49	221 (0.3)	66 (13)	46.6	1.05 (0.88-1.27)	1.10 (0.90-1.33)
Skin	C43, C44	1035 (1.6)	73 (11)	47.2	0.92 (0.86-0.99)	0.92 (0.85-0.99)
Breast	C50	4452 (7.0)	63 (13)	99.1	1.08 (1.03-1.13)	1.08 (1.03-1.13)
Cervix uteri	C53	646 (1.0)	54 (15)	100	1.12 (1.00-1.27)	1.13 (1.00-1.27)
Corpus uteri	C54	825 (1.3)	60 (12)	100	0.99 (0.88-1.11)	1.00 (0.89-1.12)
Ovary	C56	522 (0.8)	59 (13)	100	0.98 (0.85-1.12)	0.98 (0.85-1.12)
Prostate	C61	8371 (13.2)	71 (7)	0	1.07 (1.05-1.10)	1.07 (1.04-1.09)
Kidney	C64	1178 (1.9)	66 (10)	28.4	1.00 (0.94-1.07)	1.00 (0.93-1.07)
Renal pelvis and ureter	C65, C66	666 (1.1)	72 (9)	30.9	1.06 (0.96-1.17)	1.05 (0.95-1.16)
Bladder	C67	3292 (5.2)	71 (10)	18.2	1.04 (1.00-1.08)	1.04 (1.00-1.08)
Brain and nerve system	C70-C72	383 (0.6)	64 (14)	37.6	0.93 (0.80-1.07)	0.93 (0.80-1.09)
Thyroid	C73	656 (1.0)	62 (13)	74.8	0.92 (0.82-1.03)	0.92 (0.81-1.03)
Malignant lymphoma	C81-C85, C96	2177 (3.4)	69 (12)	43.0	1.02 (0.96-1.08)	1.02 (0.97-1.08)
Multiple myeloma	C88, C90	469 (0.7)	71 (10)	48.6	0.89 (0.79-1.01)	0.88 (0.78-1.00)
Leukemia	C91-C95	616 (1.0)	69 (12)	39.4	1.01 (0.91-1.11)	1.01 (0.91-1.11)

Abbreviations: CI, confidence interval; *ICD-10*, *International Classification of Diseases, Tenth Revision*; SD, standard deviation.
[a]Odds ratios and 95% CIs at the 10 drink-year point were estimated with conditional logistic regression, which was matched for sex, age, admission date, and hospital and adjusted for smoking history and occupational class. A continuous drink-year variable and restricted cubic spline methods were used.
[b]Additionally adjusted for lifestyle-related comorbidities (hypertension, hyperlipidemia, diabetes, hyperuricemia, and obesity).
[c]The total number of 63,232 includes the cases from other sites, which are not shown in the specific sites.

age (in the same 1-year age category), admission date (in the same financial year), and admitting hospital (in the same admitting hospital). Controls were those who were admitted to the hospital for the first time, and those who were later hospitalized for cancer were not eligible to be cases. The matched basic backgrounds were balanced entirely between the cases and controls: the percentage of female patients was 34.7% (21,910 of 63,232), and the mean age was 69 years (standard deviation, 10 years) for both the cases and the controls (Table 2).

Total Amount of Lifetime Alcohol Consumption and Other Covariates

According to the methodology used in previous studies that measured the total amount of lifetime alcohol consumption,[21-24] we generated a continuous drink-year variable for each patient by multiplying the average of the daily amount of standardized alcohol units (drinks per day) and the duration of drinking (years). All study subjects reported their average daily amount of standardized alcohol units and duration of drinking on admission to the hospital (or during their hospital stay due to their acute symptoms). One standardized drink containing 23 g of ethanol was equivalent to one 180-mL cup (6 ounces) of Japanese sake, one 500-mL bottle (17 ounces) of beer, one 180-mL glass (6 ounces) of wine, or one 60-mL cup (2 ounces) of whiskey.[16,17,25-28] The duration of drinking accounted for the years from the age of starting drinking up to the age of quitting drinking or the age on admission if they had not quit drinking. In addition, we categorized patients into 6 categories by their drink-year levels (0 [lifetime abstainer], >0-20, >20-40, >40-60, >60-90, and >90 drink-years). Lifetime abstainers of drinking were defined as those who responded that they had never consumed alcohol.

In addition to basic background characteristics (sex, age, admission date, and admitting hospital), confounding variables included smoking history (never, former, or current) and high occupational class status (defined by the longest held jobs in managerial/professional occupations).[25-28] Other possible mediating variables included lifestyle-related comorbidities (hypertension, hyperlipidemia, diabetes, hyperuricemia, and obesity) that are potentially linked to alcohol consumption and might explain alcohol-related cancer risk.[17,27,29]

TABLE 2. Baseline Characteristics of Overall Cancer Cases and Their Matched Controls

Characteristic	Control (n = 63,232)[a]	Case (n = 63,232)
Women, No. (%)	21,910 (34.7)	21,910 (34.7)
Age, mean (SD), y	69 (10)	69 (10)
Year, mean (SD)	2010 (3)	2010 (3)
Drinking history, No. (%)[b]		
Never	27,833 (44.0)	25,353 (40.1)
Former	7144 (11.3)	8220 (13.0)
Current	28,255 (44.7)	29,659 (46.9)
Average drinks/d, mean (SD)[b]	0.8 (1.0)	0.9 (1.1)
Duration of drinking (continuous), mean (SD), y[b]	23.5 (23.0)	25.1 (22.8)
Duration of drinking (categorical), No. (%)[b]		
Never	27,833 (44.0)	25,353 (40.1)
>0-19 y	2331 (3.7)	2408 (3.8)
20-39 y	10,077 (15.9)	10,905 (17.2)
≥40 y	22,991 (36.4)	24,566 (38.9)
Total amount of lifetime drinking (continuous), mean (SD), drink-y[b]	33.7 (44.9)	38.1 (47.4)
Total amount of lifetime drinking (categorical), No. (%)[b]		
Never	27,833 (44.0)	25,353 (40.1)
>0-20 drink-y	4234 (6.7)	4143 (6.6)
>20-40 drink-y	7972 (12.6)	7966 (12.6)
>40-60 drink-y	10,847 (17.2)	11,240 (17.8)
>60-90 drink-y	5667 (9.0)	6368 (10.1)
>90 drink-y	6679 (10.6)	8162 (12.9)
Smoking history, No. (%)[b]		
Never	27,849 (44.0)	24,247 (38.3)
Former	21,641 (34.2)	22,558 (35.7)
Current	13,742 (21.7)	16,427 (26.0)
Smoking, log(pack-y), mean (SD)[b]	1.8 (1.8)	2.1 (1.8)
High occupational class, No. (%)[b]	9167 (14.5)	8715 (13.8)
Hypertension, No. (%)	23,105 (36.5)	23,286 (36.8)
Hyperlipidemia, No. (%)[b]	7695 (12.2)	7388 (11.7)
Diabetes, No. (%)[b]	10,324 (16.3)	9573 (15.1)
Hyperuricemia, No. (%)[b]	2131 (3.4)	1942 (3.1)
Obesity, No. (%)	7601 (12.0)	7596 (12.0)

Abbreviation: SD, standard deviation.
[a]Controls were matched for sex, age, admission date, and admitting hospital.
[b]$P < .05$ for *t* test or chi-square test.

Statistical Analysis

The odds ratios (ORs) and 95% confidence intervals (CIs) for overall cancer incidence were estimated against continuous drink-year levels by conditional logistic regression matched for sex, age, admission date, and admitting hospital with a restricted cubic spline method knotted at 0, 23, and 96 drink-years (corresponding to the 10th, 50th, and 90th percentile points, respectively) on the basis of the distribution of our data.[30,31] Lifetime abstainers with 0 drink-years served as the referent group for all analyses. To control for potential confounding and mediating variables, we mutually adjusted for smoking history and occupational class (model 1), and we made additional adjustments for comorbidities (model 2). The OR and 95% CI for each drink-year category (>0-20, >20-40, >40-60, >60-90, and >90 drink-years) were also estimated. For specific cancer incidence, we restricted analyses to each cancer site and performed the same analytic procedure.

In sensitivity analyses, we estimated ORs and 95% CIs for men and women, current and former drinkers, and those who drank for <20, 20 to 39, and ≥40 years. In addition, we stratified analyses by occupational class (high vs low) because of occupational class inequalities in cancer risk.[25-27] Furthermore, we restricted analyses to never smokers because of potential synergy effects of smoking and drinking.[17,32] Lifetime abstainers with 0 drink-years served as the referent group for all analyses. In addition, we used alternative control groups (all available hospital controls diagnosed with benign diseases) as well as alternative drinking categories, which included 7 joint categories for the daily amount and duration of drinking (0 drinks per day [lifetime abstainer], ≤2 drinks per day and <20 years, ≤2 drinks per day and 20-39 years, ≤2 drinks per day and ≥40 years, >2 drinks per day and <20 years, >2 drinks per day and 20-39 years, and >2 drinks per day for ≥40 years). In these sensitivity analyses, we analyzed only overall cancer risk because of the limitation of our sample size. α was set at .05, and all *P* values were 2-sided. Data were analyzed with STATA/MP13.1 (StataCorp LP, College Station, Texas).

RESULTS

Overall, the cases tended to drink more than the controls (Table 2): the prevalence of ever drinkers among the cases and controls was 59.9% and 56.0%, respectively ($P < .001$), and the mean drink-years for the cases and controls were 38.1 and 33.7, respectively ($P < .001$). In comparison with the controls, smoking behavior was more prevalent, and a high occupational class was less prevalent among the cases (Table 2). Except for nonsignificant associations in hypertension and obesity, comorbidities were slightly less prevalent in the cases versus the controls. As a result, compared with lifetime abstainers, ever drinkers showed increased odds for aerodigestive and gastrointestinal cancers (oral, laryngeal, esophageal, stomach, colorectal, and liver cancers) as well as breast and prostate cancers; this was most pronounced for esophageal cancer (Fig. 1).

For overall cancer risk, cubic spline curves showed a dose-response, slightly convex shape (but almost a linear shape up to 20 drink-years) against light to moderate drink-year levels, with the minimum risk at 0 (Fig. 2). The observed association persisted even after we had fully controlled for comorbidities (model 2): the OR at 10 drink-years was 1.05 (95% CI, 1.04-1.06; Table 1). Compared with lifetime abstainers, the odds were elevated across all levels of categorical drink-years (Table 3), and the elevated odds persisted even after we had fully

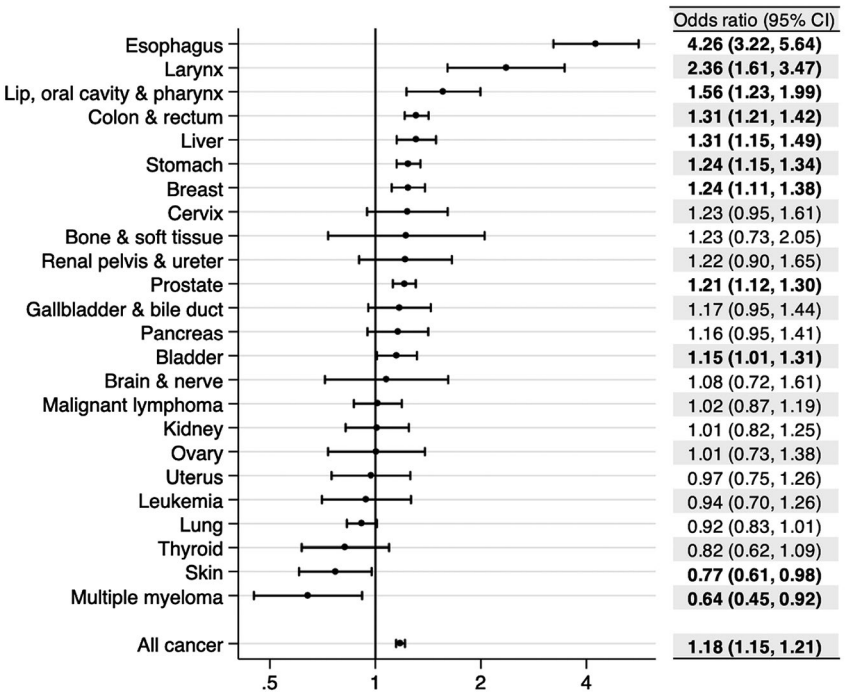

Figure 1. Overall and specific cancer incidence risk associated with ever drinkers. Odds ratios (dots) and 95% CIs (lines) were estimated with 63,232 cases and 63,232 controls by conditional logistic regression matched for sex, age, admission date, and hospital. Smoking history, occupational class, and comorbidities were mutually adjusted. Bolding indicates $P < .05$. CI indicates confidence interval.

controlled for comorbidities (model 2): the OR for >0 to 20 drink-years was 1.06 (95% CI, 1.01-1.11). Those who drank 2 drinks or fewer per day had elevated odds for overall cancer risk across all duration-of-drinking categories (Table 3).

For specific cancer sites, most gastrointestinal and upper aerodigestive cancers (including oral, esophageal, stomach, colorectal, liver, gallbladder, and laryngeal cancers) as well as breast and prostate cancers showed the same pattern (slightly convex or linear shapes) at light to moderate drink-year levels (Fig. 3 and Tables 2 and 3); this was most pronounced for esophageal cancer (OR at 10 drink-years, 1.44; 95% CI, 1.33-1.57; model 2; Table 2). Pancreatic, cervical, renal pelvis and ureter, and bladder cancers as well as bone and soft-tissue cancers showed a hint of a potential linear association (Fig. 3). No protective association (but a potential linear association) was observed in kidney cancer, whereas light to moderate alcohol consumption was potentially associated with a reduced risk for skin cancer and multiple myeloma (Fig. 3).

In sensitivity analyses, the patterns were mostly identical, regardless of sex, drinking habits, drinking durations, or occupational classes (Fig. 2 and Supporting Table 1). The patterns were mostly identical in the analyses with never smokers (Supporting Fig. 1 and Supporting Table 1) and alternative control groups (Supporting Fig. 2).

DISCUSSION

In Japan, overall cancer risk appeared to be the lowest at zero alcohol consumption, with a modest increase in overall cancer risk at light to moderate levels for the total amount of lifetime alcohol consumption. A dose-response, almost linear association was observed for overall cancer risk and lifetime alcohol consumption without any thresholds, and this suggested that a light level of drinking at the 10-drink-year point would increase overall cancer risk by 5%. Although the impact of lifetime alcohol consumption varied across each cancer site, the elevated overall cancer risk appeared to be explained by alcohol-related cancer risk across relatively common sites, including the colorectum, stomach, breast, prostate, and esophagus.[32] Besides, the risk associated with light to moderate levels for the total amount of lifetime alcohol consumption appeared to similarly matter across sexes and different drinking and smoking behaviors or occupational classes in that country.

Our observed patterns of alcohol-related cancer risk appear to support findings in previous studies.[6-8,12,13]

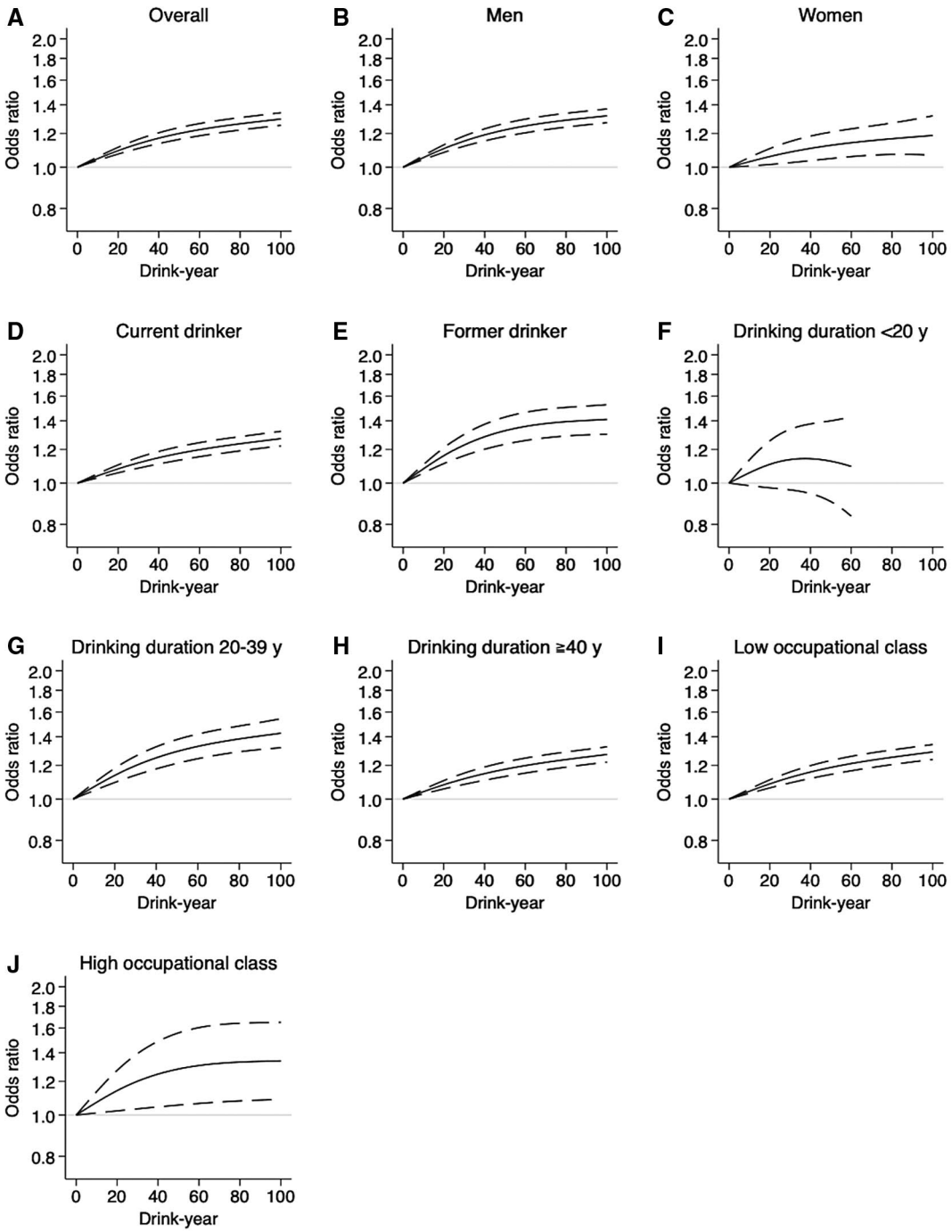

Figure 2. Cubic spline curves for overall cancer risk against the total amount of lifetime alcohol consumption. Odds ratios (solid lines) and 95% confidence intervals (dashed lines) were estimated by conditional logistic regression matched for sex, age, admission date, and hospital. Smoking history and occupational class were mutually adjusted. The numbers of subjects used for the analyses were as follows: (A) 126,464 (overall), (B) 82,644 (men), (C) 43,820 (women), (D) 98,286 (current drinkers), (E) 45,470 (former drinkers), (F) 37,762 (those who drank <20 years), (G) 53,804 (those who drank 20-39 years), (H) 86,290 (those who drank ≥40 years), (I) 93,826 (those in a low occupational class), and (J) 3126 (those in a high occupational class).

For upper aerodigestive and gastrointestinal cancers, our observed patterns would be plausible because of the common genetic vulnerability to acetaldehyde in the Japanese.[12] Acetaldehyde is carcinogenic via multiple mechanisms (eg, stimulating cell proliferation and inducing DNA damage) and increases cancer risk even with light

TABLE 3. Odds Ratios for Overall and Specific Cancer Incidence Estimated With the Categorical Total Amount of Lifetime Alcohol Consumption

Characteristic		Odds Ratio (95% CI)	
		Model 1[a]	Model 2[b]
Drink-y (vs lifetime abstainers)			
Overall	>0-20 drink-y	1.06 (1.01-1.12)	1.06 (1.01-1.11)
	>20-40 drink-y	1.13 (1.08-1.17)	1.12 (1.08-1.17)
	>40-60 drink-y	1.18 (1.13-1.22)	1.18 (1.13-1.22)
	>60-90 drink-y	1.26 (1.21-1.32)	1.26 (1.21-1.32)
	>90 drink-y	1.37 (1.31-1.43)	1.37 (1.31-1.43)
Esophagus	>0-20 drink-y	1.72 (1.06-2.79)	1.78 (1.09-2.90)
	>20-40 drink-y	2.78 (1.97-3.93)	2.74 (1.94-3.88)
	>40-60 drink-y	4.25 (3.08-5.88)	4.13 (2.98-5.71)
	>60-90 drink-y	5.31 (3.79-7.43)	5.23 (3.72-7.35)
	>90 drink-y	7.17 (5.17-9.96)	7.03 (5.04-9.80)
Stomach	>0-20 drink-y	1.09 (0.95-1.25)	1.09 (0.95-1.26)
	>20-40 drink-y	1.17 (1.05-1.30)	1.17 (1.05-1.30)
	>40-60 drink-y	1.21 (1.10-1.33)	1.22 (1.10-1.34)
	>60-90 drink-y	1.35 (1.21-1.52)	1.36 (1.21-1.52)
	>90 drink-y	1.43 (1.28-1.60)	1.44 (1.29-1.61)
Colon and rectum	>0-20 drink-y	1.14 (1.00-1.30)	1.14 (1.00-1.30)
	>20-40 drink-y	1.12 (1.01-1.25)	1.12 (1.01-1.25)
	>40-60 drink-y	1.29 (1.17-1.43)	1.29 (1.16-1.43)
	>60-90 drink-y	1.56 (1.39-1.76)	1.55 (1.38-1.75)
	>90 drink-y	1.69 (1.51-1.90)	1.69 (1.50-1.89)
Liver	>0-20 drink-y	1.13 (0.91-1.41)	1.19 (0.95-1.49)
	>20-40 drink-y	1.22 (1.02-1.44)	1.28 (1.07-1.53)
	>40-60 drink-y	1.10 (0.94-1.29)	1.11 (0.94-1.31)
	>60-90 drink-y	1.44 (1.19-1.76)	1.46 (1.19-1.79)
	>90 drink-y	1.64 (1.38-1.95)	1.68 (1.41-2.01)
Breast	>0-20 drink-y	1.29 (1.12-1.50)	1.29 (1.11-1.49)
	>20-40 drink-y	1.26 (1.08-1.47)	1.25 (1.07-1.46)
	>40-60 drink-y	1.05 (0.83-1.33)	1.05 (0.83-1.33)
	>60-90 drink-y	1.42 (1.00-2.04)	1.43 (1.00-2.05)
	>90 drink-y	1.30 (0.86-1.96)	1.27 (0.84-1.92)
Prostate	>0-20 drink-y	1.17 (1.01-1.35)	1.16 (1.00-1.34)
	>20-40 drink-y	1.23 (1.11-1.36)	1.22 (1.10-1.35)
	>40-60 drink-y	1.27 (1.16-1.38)	1.25 (1.14-1.37)
	>60-90 drink-y	1.28 (1.14-1.43)	1.25 (1.12-1.40)
	>90 drink-y	1.14 (1.03-1.26)	1.11 (1.00-1.24)
Joint category with daily amount and duration of drinking (vs lifetime abstainers)			
Overall	≤2 drinks/d and <20 y	1.10 (1.03-1.17)	1.10 (1.03-1.17)
	≤2 drinks/d and 20-39 y	1.18 (1.13-1.23)	1.18 (1.13-1.23)
	≤2 drinks/d and ≥40 y	1.16 (1.12-1.20)	1.16 (1.12-1.19)
	>2 drinks/d and <20 y	1.05 (0.86-1.29)	1.05 (0.85-1.29)
	>2 drinks/d and 20-39 y	1.41 (1.29-1.53)	1.41 (1.30-1.53)
	>2 drinks/d and ≥40 y	1.54 (1.44-1.64)	1.54 (1.44-1.64)

Abbreviation: CI, confidence interval.
[a]Conditional logistic regression matched for sex, age, admission date, and hospital and adjusted for smoking history and occupational class.
[b]Additionally adjusted for lifestyle-related comorbidities (hypertension, hyperlipidemia, diabetes, hyperuricemia, and obesity).

levels of lifetime alcohol consumption, regardless of race or region of the world.[6-10,13,14] In the current study, even light to moderate levels of lifetime alcohol consumption appeared to increase most of the upper aerodigestive and gastrointestinal cancers.[9,12,14] In contrast to the patterns observed in Western settings,[1-3] we observed no protective effects of light to moderate lifetime alcohol consumption for colorectal and kidney cancers. For breast and prostate cancer, different pathways such as elevations of circulating sex hormone levels (ie, estrogens and androgens) by alcohol use may explain the alcohol-related cancer risk at even light to moderate levels of lifetime alcohol consumption.[10,13] In the JPHC study, a dose-response trend between alcohol consumption and advanced prostate cancer risk (P for trend = .02) was reported.[10] As yet, evidence for potential mechanisms that may explain reduced odds for skin cancer and multiple myeloma remains scarce. The potential causal (biologically protective effect) and noncausal explanations (unmeasured confounding) remain unclear for these inverse associations.

The limitations of the current study should be noted. First, the selection of hospital controls may have introduced a selection bias toward the null. Although sensitivity analyses with different drinking behaviors showed almost identical patterns, the lifetime drinking history recalled at the time of hospital admission (ie, not obtained on multiple occasions before the onset of disease) may be subject to recall bias. In addition, our exposure assessment did not inquire about starting/ending dates of drinking habits. Indeed, our observed odds for overall cancer risk (a 5% increase by 10 drink-years) was roughly equivalent to half of the risk observed in a previous study from the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial in the United States (a 10% increase by the lifetime average of 5 drinks per day).[8] Therefore, our observed cancer risk associated with light to moderate lifetime alcohol consumption would be underestimated. Second, because of the limitation of our data set, we could not assess alcohol-related cancer risk by different types of alcoholic beverages (eg, Japanese sake, beer, wine, and whiskey). However, studies suggest that the ethanol (but not the other components of alcoholic beverages) matters primarily for cancer risk, regardless of the types of alcoholic beverages.[9] In addition, we could not assess other explanatory variables such as menopausal hormone therapy (for female breast cancer), a family history of cancer, diet (eg, coffee and red meat), physical activities, and ALDH2 genotypes.[9,14,33] In the JPHC study, alcohol-related bladder cancer risk was observed in male "flushers" (who are supposed to have polymorphisms in ALDH2 enzyme) but not in male nonflushers.[9] In the assessment of how robust our estimate (OR for ever drinkers, 1.18) was to potential unmeasured and uncontrolled confounding, the E-value was 1.64.[34] This means that there

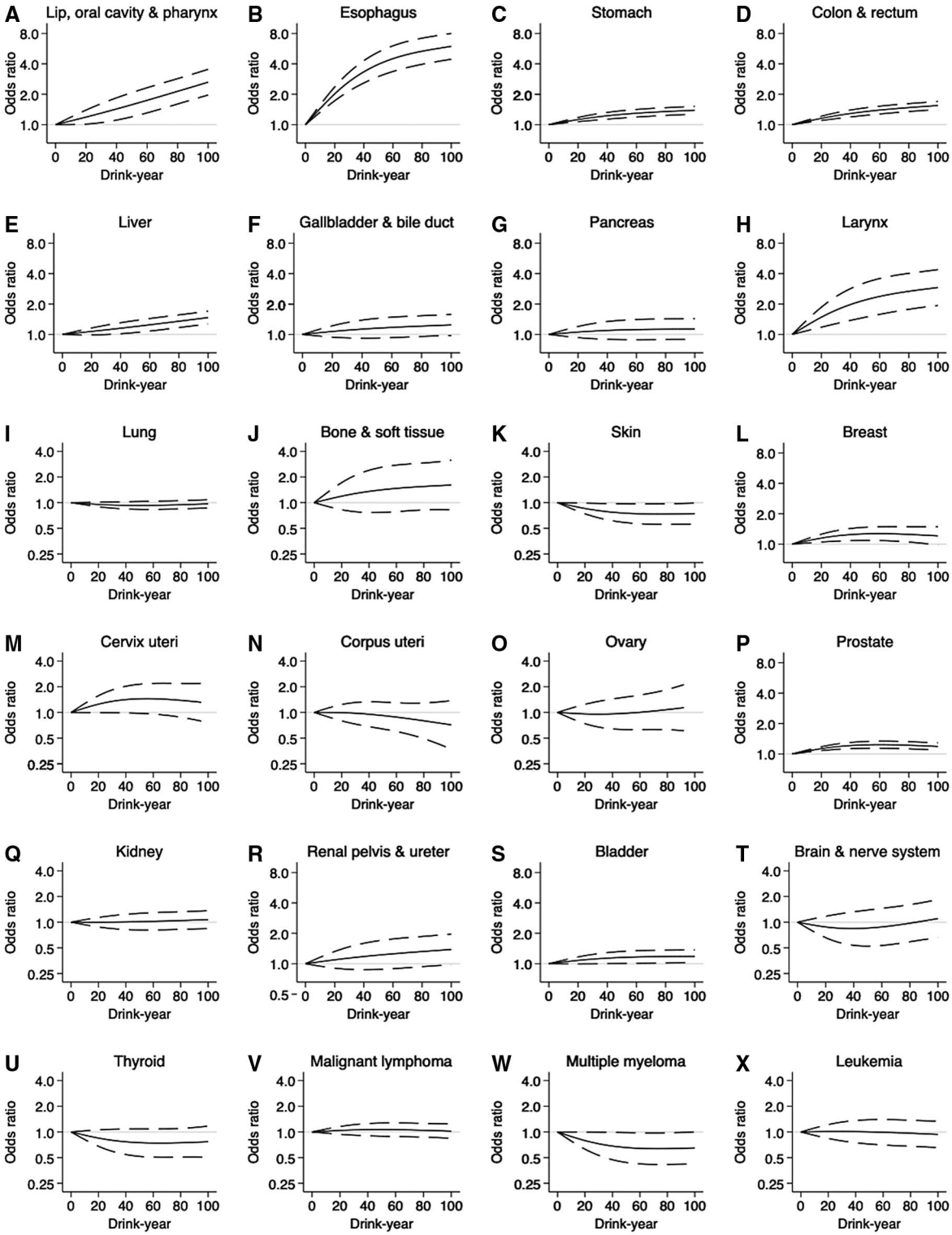

Figure 3. Cubic spline curves for specific cancer risks against continuous total amount of lifetime alcohol consumption. ORs (solid line) and 95% CIs (dashed line) were estimated by conditional logistic regression, mutually adjusted for smoking history, occupational class, and comorbidities. The numbers of subjects used for the analyses were as follows: (A) 2090 (Lip, oral cavity, and pharynx), (B) 2,816 (Esophagus), (C) 18,710 (Stomach), (D) 19,274 (Colon and rectum), (E) 7208 (Liver), (F) 2700 (Gallbladder and bile duct), (G) 2992 (Pancreas), (H) 1098 (Larynx), (I) 11,944 (Lung), (J) 442 (Bone and soft tissue), (K) 2070 (Skin), (L) 8904 (Breast), (M) 1292 (Cervix uteri), (N) 1650 (Corpus uteri), (O) 1044 (Ovary), (P) 16,742 (Prostate), (Q) 2356 (Kidney), (R) 1332 (Renal pelvis and ureter), (S) 6584 (Bladder), (T) 766 (Brain and nerve system), (U) 1312 (Thyroid), (V) 4354 (Malignant lymphoma), (W) 938 (Multiple myeloma), and (X) 1232 (Leukemia).

would need to be at least a 1.64-fold association between an unobserved confounder and the exposure/outcome to explain the observed association. Third, although we controlled for smoking in regression analyses, a limited number of cases did not allow us to restrict all analyses within never smokers, and residual smoking effects might have persisted in our results. Despite these limitations, we have demonstrated a comprehensive picture of significant overall cancer risk and risks of various cancers associated with light to moderate levels for the total amount of lifetime alcohol consumption in Japan with a restricted cubic spline method and a clinically useful indicator of drinking intensity. The strengths also include the size of this study, one of the largest multicenter studies for alcohol-related cancer risk reported in that country,[9-11] and accurate diagnoses directly extracted from medical charts.

Inoue et al[32] reported that the population attributable risk for overall cancer incidence by alcohol (9.0% in men and 2.5% in women) was smaller than the risk due to tobacco smoking (29.7% in men and 5.0% in women) and infections such as *Helicobacter pylori*, hepatitis B virus, and hepatitis C virus (22.8% in men and 17.5% in women), the 2 major prioritized preventable risk factors in Japan. Among alcohol-related cancer cases, the highest population attributable risk was due to upper digestive cancer,[5] which is not one of the most common types in Japan.[25,26] In addition, benefits of adequate, nonheavy alcohol drinking have been reported for overall mortality as well as cardiovascular health.[8] However, we observed modest alcohol-related cancer risk in the most common types (colorectal, stomach, breast, prostate, and liver cancers) even at light to moderate levels of lifetime alcohol consumption in Japan. Thus, given the current burden of overall cancer incidence, we should further encourage promoting public education about alcohol-related cancer risk.

In summary, we have documented various cancer risks associated with even light to moderate levels for the total amount of lifetime alcohol consumption in Japan, with the minimum risk at zero consumption. The current national cancer control strategy needs to strengthen the emphasis on moderating drinking behavior in the Japanese population to reduce the burden of cancer incidence.

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CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

AUTHOR CONTRIBUTIONS

Masayoshi Zaitsu: Conception and design; development of methodology; acquisition of data; analysis and interpretation of data; study supervision; writing, review, and/or revision of the manuscript; and administrative, technical, or material support. **Takumi Takeuchi:** Acquisition of data; writing, review, and/or revision of the manuscript; and administrative, technical, or material support. **Yasuki Kobayashi:** Study supervision; writing, review, and/or revision of the manuscript; and administrative, technical, or material support. **Ichiro Kawachi:** Conception and design; development of methodology; study supervision; writing, review, and/or revision of the manuscript; and administrative, technical, or material support.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the Japan Organization of Occupational Health and Safety. Restrictions apply to the availability of these data, which were used under license for this study; research data are not shared. If any person wishes to verify the data, they are most welcome to contact the corresponding author.

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ORIGINAL RESEARCH

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Occupational disparities in bladder cancer survival: A population-based cancer registry study in Japan

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Abstract

Background: Little is known about occupational disparities in bladder cancer survival.

Methods: Using data from a population-based cancer registry (1970-2016), we identified 3593 patients with incident bladder cancer diagnosed during 1970-2011 who completed occupational information. The patients were followed for 5 years (median follow-up time 5.0 years). Their longest-held occupations at incident bladder cancer diagnosis were classified according to a national standardized classification. Hazard ratios (HRs) and 95% confidence intervals (CIs) for overall death were estimated by Cox proportional hazard model, adjusted for age, sex, and year of diagnosis. Clerical workers served as the reference group.

Results: Overall prognosis was fair in this population (5-year overall survival, 61.9%). Compared with patients in clerical jobs, survival was poorer for those in professional and managerial jobs (mortality HR 1.36; 95% CI 1.09-1.69), sales and service jobs (HR 1.25, 95% CI 1.01-1.56), construction jobs (HR 1.83, 95% CI 1.40-2.38), and manufacturing jobs (HR 1.32, 95% CI 1.05-1.66), as well as those not actively employed (HR 1.27, 95% CI 1.02-1.58). A similar pattern was observed in the subgroup analyses restricted to male patients as well as additional analyses adjusted for potential prognostic variables (eg, stage) with multiple imputation.

Conclusion: We documented occupational disparities in bladder cancer survival in Japan. However, the pattern of disparity did not favor highest occupational groups.

KEYWORDS

bladder cancer, Japan, occupation, population-based, socioeconomic status, survival

1 | INTRODUCTION

Bladder cancer, which is four times more common in men compared with women, is the ninth most common cancer worldwide, and in 2012, male and female age-standardized incidence rates were, respectively, 9.6 and 2.2 per 100 000 population in Japan.[1] Although bladder cancer incidence in Japan is lower compared with that in Western countries, it is the highest in the East-Asian region.[1]

The two most common risk factors for bladder cancer are smoking and occupational exposures to carcinogens.[2] Smoking approximately quadruples the risk, and 50% of new bladder cancer cases are attributable to smoking.[3] Occupational exposure to carcinogens (specifically, aromatic amines) is known to increase bladder cancer risk in occupations such as dye-making, tobacco, rubber, and leather workers, printers, and hairdressers.[2,4-6] In Japan, an epidemic of bladder cancer incidence caused by exposure to ortho-toluidine was reported in dye-making workers,[7] and ortho-toluidine-related bladder cancer has been designated as an occupational disease. Fortunately, occupational regulations have reduced this source of exposure in most countries.[2]

However, occupational differences in bladder cancer *survival* remain sparsely documented. In the Western context, several studies suggested that bladder cancer patients from blue-collar job backgrounds (eg, manufacturing and mining) had a worse prognosis compared with white-collar counterparts (eg, professionals and managerial workers).[8-10] Clinical and pathological features (eg, pathology, stage, and treatment), as well as smoking behavior and environmental factors, are thought to underlie this monotonic pattern of occupational gradient in survival: that is, higher occupational class workers enjoy more favorable bladder cancer survival.[6,8-10] Yet, to the best of our knowledge, no studies have evaluated occupational disparities in bladder cancer survival in the non-Western setting. In addition, in Japan, working in managerial and professional positions, the highest occupational class background, may not guarantee the best health outcome in all-cause and cancer-specific mortality and cardiovascular risks,[11-13] which contrasts with the monotonic occupational gradient widely seen in the Western setting.

Accordingly, the goal of this study was to elucidate the association between occupation and bladder cancer survival in Japan. Using a population-based cancer registry data set of bladder cancer, we primarily examined whether occupational disparities exist in bladder cancer survival with a monotonic occupational gradient. Additionally, we examined whether the observed disparities persist even after controlling for potential prognostic variables including clinicopathological features and smoking history.

2 | MATERIALS AND METHODS

2.1 | Data setting

We conducted a 5-year overall survival analysis for bladder cancer patients diagnosed during 1970-2011, using a population-based data set (1970-2016) of Kanagawa Cancer Registry (KCR), which covers the population of over nine million in Kanagawa Prefecture, representing 7% of the Japanese national population. Details of the study database have been previously described.[14,15] Briefly, Kanagawa Prefecture, a metropolitan prefecture located next to Tokyo, is the second largest prefecture in Japan, and KCR is one of the largest population-based cancer registries in Japan. The data include basic information (sex, age, date of diagnosis, date of death/last follow-up), and clinical information (pathology, stage, treatment). Additionally, KCR partly collected occupational and smoking history at diagnosis among the bladder cancer patients during 1970-2011. However, on average, only 15% of the annually registered bladder cancer patients completed occupational information, and 19% completed smoking information; these data were no longer collected after 2016 due to the change of data management practice.[14] KCR automatically updates dates of death/last follow-up with population registers and death certificates, and previous diagnostic codes are updated to be consistent with changes in coding practice.[14,15] The occupational distribution in KCR parallels the national statistics as well as previous studies in Japan.[13,14,16-18] We obtained a de-identified data set under the research agreement between the authors and KCR, and the research ethics committees of The University of Tokyo, Tokyo (Protocol Number 3891-4), and Kanto Rosai Hospital, Kanagawa (Protocol Number 2014-38) approved the study.

2.2 | Main outcome and study subjects

The main outcome was overall survival, defined by the person-years from the date of initial bladder cancer diagnosis to the date of death/last follow-up.

From a total of 23 906 bladder cancer patients registered in KCR with a diagnosis of incident bladder cancer (C67 in International Classification of Diseases, 10th revision) between 1970 and 2011, we excluded those with missing data for occupational information (20 313 patients, 85.0%), yielding an analytic sample of 3593 bladder cancer patients who had complete occupational information for analysis. The geographical locations of the study subjects varied from urbanized to rural areas. The occupational distribution of the analytic samples paralleled the national statistics as well as previous studies in Japan.[13,14,16-18]

2.3 | Occupational class

From the longest-held occupation at incident bladder cancer diagnosis listed in KCR based on the Japan Standard Occupational Classification, we identified major occupational categories for each patient as follows[13,14,16-18]: (a) professional and managerial workers, (b) clerical workers, (c) sales and service workers (including security, cleaning, carrying, and packaging workers), (d) agriculture, forestry, and fishery workers, (e) transportation workers (including machine operation workers), (f) construction and mining workers, (g) manufacturing workers, and (h) those not actively engaged in paid employment (eg, homemakers, students, unemployed, miscellaneous workers).

2.4 | Covariates

Covariates included basic characteristics (sex, age, and year of diagnosis) as confounding factors (Figure 1). We adjusted for year of diagnosis as a continuous variable to control for potential secular changes in treatment regimens.[14] Additionally, in a supplemental analysis, known prognostic factors were included in the regression analyses as potential mediating variables that may *explain* occupational disparities of bladder cancer survival (Figure 1)[10,15]: summary stage (localized [early stage] vs regional invasion and distant metastasis [late stage]), pathological type (identified by International Classification of Disease for Oncology, Third edition pathological codes; urothelial carcinoma [8120-8131 and 8050] vs non-urothelial carcinoma), pathological grade (grade 3 or 4 [high-grade] vs grade 1 or 2 [low-grade]), surgery (yes/no), and smoking behaviors (never/ever). Due to the limitation in the data availability of the Union for International Cancer Control TNM staging information, we defined early (0, I) and late (II-IV) stages in the subgroup analysis of bladder cancer patients after 2003.[14,15]

2.5 | Statistical analysis

The 5-year overall survival rates were estimated by the Kaplan-Meier curves and compared by logrank test. In our main analytic model (model 1), among the 3593 bladder cancer patients who completed occupational information, hazard ratios (HRs) and 95% confidence intervals (CIs) for overall death were estimated by Cox proportional hazard model, minimally adjusted for basic characteristics (sex, age, and year of diagnosis). Clerical workers served as the reference group for all analyses. For sensitivity analyses, to improve the completing rate on occupational information (15%), we performed subgroup analyses among (a) all male patients (n = 3278), the completing rate was 18% (3278 out of all 18 272 male bladder cancer patients during the study period) and (b) male patients aged < 70 (n = 1900), the completing rate was 24% (1900 out of all 7961 male bladder cancer patients aged < 70 during the study period). Additionally, we restricted analyses to a cohort of 826 bladder cancer patients diagnosed after 2003 with TNM staging information.

In a supplementary analysis to explain observed occupational differences in bladder cancer survival, we maximally adjusted for stage, pathology, treatment, and smoking behaviors. However, in this regression analysis among the 3593 study subjects, records included a large number of missing data: 88.1% (3165 patients) of stage information, 12.5% (448 patients) of pathological type, 79.2% (2846 patients) of pathological grade, 1.6% (57 patients) of treatment, and 72.3% (2596 patients) of smoking behaviors. We conducted multiple imputation for missing data among the 3593 study subjects with all variables used for analysis, and 20 imputed data sets were generated.[14] Additionally, we estimated HRs and 95% CIs with multiple imputation among all 23 906 bladder cancer patients registered in KCR in the study period.

Alpha was set at 0.05, and all *P*-values were two-sided. Data were analyzed using STATA/MP13.1 (StataCorp LP).

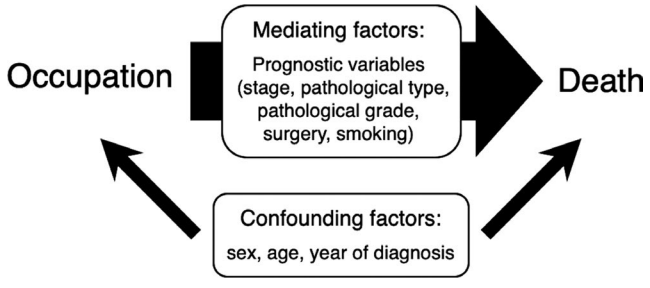

FIGURE 1 Confounding and mediating variables in the analytic model

3 | RESULTS

During the study period, the 5-year overall survival was 61.9% (Figure 2 and Table 1). Significantly poorer prognoses were observed in professional and managerial workers (HR 1.36; 95% CI 1.09-1.69), sales and service workers (HR 1.25, 95% CI 1.01-1.56), construction and mining workers (HR 1.83, 95% CI 1.40-2.38), manufacturing workers (HR 1.32, 95% CI 1.05-1.66), and those not actively employed (HR 1.27, 95% CI 1.02-1.58) compared with clerical workers (Figure 3 and Table 2). A poorer prognosis tended to be observed in agriculture, fishery, and forestry workers (HR 1.32, 95% CI 1.00-1.74) compared with clerical workers, while prognosis in transportation workers did not differ from clerical workers (Figure 3 and Table 2). The sensitivity analyses with different subgroups of bladder cancer patients showed the similar pattern (Figure 3 and Table 2).

In a supplementary analysis, although the observed occupational difference was partly attenuated after adjustment for prognostic variables, the occupational disparities remained significant for professional and managerial workers and

FIGURE 2 Overall survival curves by longest-held occupations

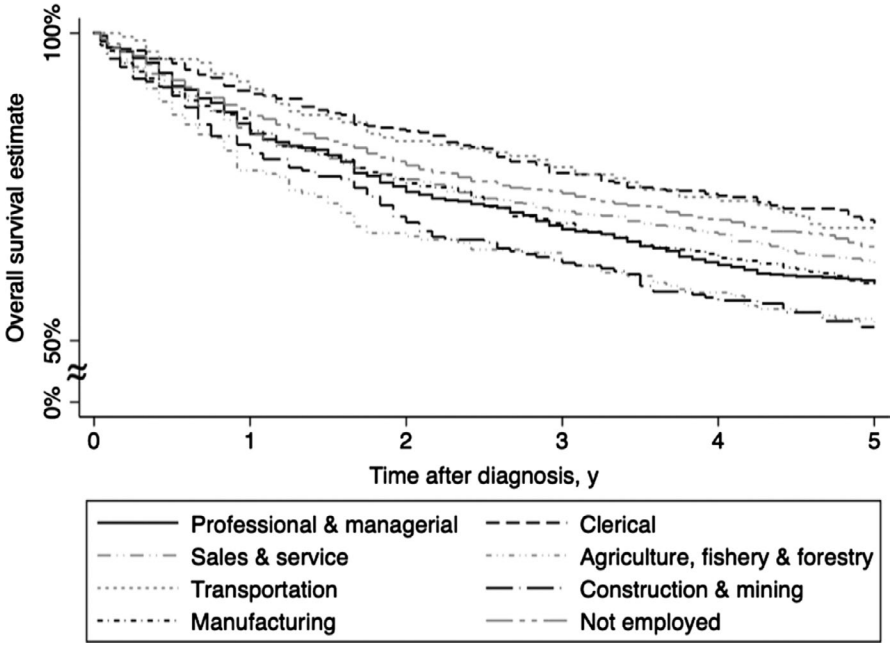

TABLE 1 Characteristics of bladder cancer patients who completed occupational information in Kanagawa Cancer Registry

Characteristics	Mean (SD) or number (%)		
	All patients, n = 3593	**Men, n = 3278**	**Men, age < 70, n = 1900**
Incidence rate, person-year	0.10	0.10	0.08
5-y survival estimate, %	61.9%	61.7%	69.7%
Women	315 (8.8%)	0 (0.0%)	0 (0.0%)
Age, y	67 (11)	67 (11)	59 (8)
Year of diagnosis	1995 (9)	1995 (9)	1994 (9)
Longest-held occupation			
Professional & managerial	664 (18.5%)	601 (18.3%)	335 (17.6%)
Clerical	387 (10.8%)	345 (10.5%)	216 (11.4%)
Sales & service	725 (20.2%)	593 (18.1%)	343 (18.1%)
Agriculture, fishery, and forestry	189 (5.3%)	176 (5.4%)	49 (2.6%)
Transportation	168 (4.7%)	166 (5.1%)	113 (5.9%)
Construction and mining	218 (6.1%)	213 (6.5%)	135 (7.1%)
Manufacturing	449 (12.5%)	423 (12.9%)	241 (12.7%)
Not employed	793 (22.1%)	761 (23.2%)	468 (24.6%)
Stage	n = 428	n = 388	n = 191
Late-stage	54 (12.6%)	50 (12.9%)	26 (13.6%)
Histological type	n = 3145	n = 2870	n = 1669
Non-urothelial carcinoma	190 (6.0%)	159 (5.5%)	96 (5.8%)
Pathological grade	n = 747	n = 672	n = 370
High-grade	242 (32.4%)	221 (32.9%)	127 (34.3%)
Treatment	n = 3536	n = 3228	n = 1874
Any surgery	3283 (92.8%)	2998 (92.9%)	1773 (94.6%)
Smoking behavior	n = 997	n = 910	n = 539
Ever smoker	670 (67.2%)	643 (70.7%)	402 (74.6%)

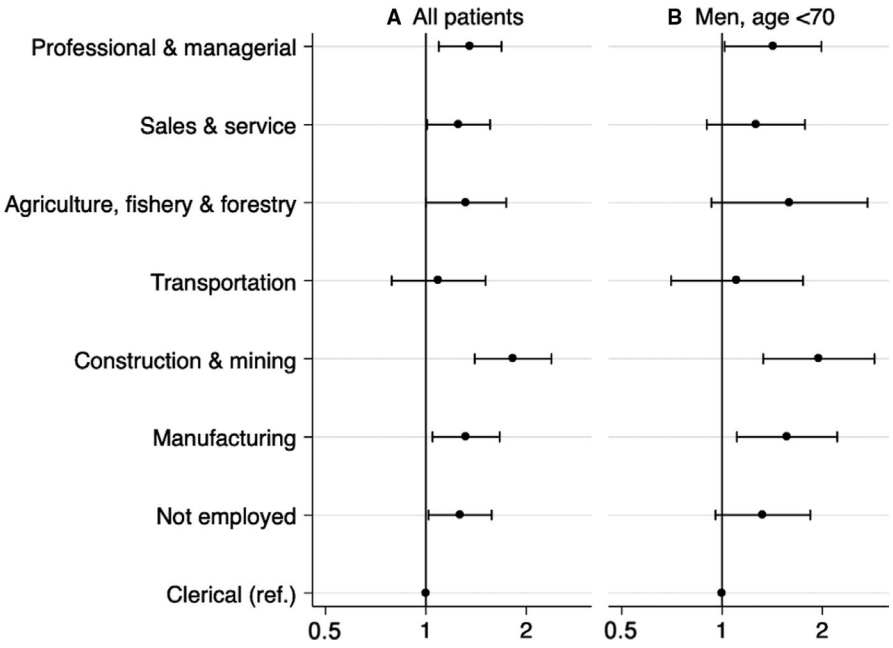

FIGURE 3 Occupational disparities in bladder cancer survival estimated with Cox proportional hazard model. Hazard ratios (circle) and 95% confidence intervals (line) were adjusted for sex, age, and year of diagnosis among (A) all study patients (n = 3593) and (B) male patients aged < 70 (n = 1900)

TABLE 2 Results of Cox proportional hazard model among bladder cancer patients with complete occupational information

	Hazard ratio (95% confidence interval)			
	1970-2016			2003-2016
Characteristics	All patients, n = 3593	Men, n = 3278	Men, age < 70, n = 1900	All patients, n = 826
Longest-held occupation				
Clerical	1.00	1.00	1.00	1.00
Professional and managerial	1.36 (1.09, 1.69)**	1.42 (1.13, 1.79)**	1.42 (1.02, 1.99)*	1.52 (0.86, 2.72)
Sales & service	1.25 (1.01, 1.56)*	1.30 (1.03, 1.64)*	1.26 (0.90, 1.77)	1.06 (0.58, 1.93)
Agriculture, fishery, and forestry	1.32 (1.00, 1.74)	1.35 (1.01, 1.80)*	1.59 (0.93, 2.74)	2.31 (1.06, 5.07)*
Transportation	1.09 (0.79, 1.51)	1.11 (0.79, 1.55)	1.11 (0.70, 1.75)	1.27 (0.54, 3.00)
Construction and mining	1.83 (1.40, 2.38)***	1.93 (1.47, 2.53)***	1.95 (1.33, 2.87)***	2.89 (1.48, 5.62)**
Manufacturing	1.32 (1.05, 1.66)*	1.31 (1.03, 1.67)*	1.57 (1.11, 2.22)*	1.88 (1.02, 3.47)*
Not employed	1.27 (1.02, 1.58)*	1.31 (1.04, 1.65)*	1.33 (0.96, 1.84)	1.16 (0.66, 2.04)
Women	1.02 (0.84, 1.24)	NA	NA	0.82 (0.51, 1.30)
Age	1.04 (1.03, 1.05)***	1.04 (1.03, 1.05)***	1.02 (1.01, 1.03)**	1.06 (1.05, 1.07)***
Year of diagnosis	0.98 (0.97, 0.99)***	0.98 (0.97, 0.98)***	0.98 (0.97, 0.99)***	0.93 (0.88, 0.99)*

*$P < .05$.
**$P < .01$.
***$P < .001$.

construction and mining workers (Table 3). The pattern was mostly similar among all bladder cancer patients registered in KCR in the study period (Table 3).

4 | DISCUSSION

As far as we are aware, our study is the first to demonstrate occupational disparities in bladder cancer survival in Japan. Contrary to expectation, we did not find a monotonic gradient in survival according to occupation, that is, professional and managerial workers experiencing the most favorable survival chances. Instead, we found that compared with clerical workers, the 5-year overall survival was worse among professional and managerial workers, as well as among construction, sales and service, and manufacturing workers, and those not actively employed. Although potential occupational disparities in prognostic factors (clinical and pathological

TABLE 3 Cox proportional hazard model with multiple imputation among bladder cancer patients in Kanagawa Cancer Registry

Characteristics	Hazard ratio (95% confidence interval)		
	Complete occupational information[a]		All bladder cancer patients[b]
	All patients (1970-2016) n = 3593	Subgroup with TNM staging (2003-2016) n = 826	All patients (1970-2016) n = 23 906
Longest-held occupation			
Clerical	1.00	1.00	1.00 (1.00, 1.00)
Professional and managerial	1.27 (1.01, 1.60)*	1.37 (0.75, 2.49)	1.19 (1.00, 1.41)*
Sales and service	1.15 (0.91, 1.44)	0.96 (0.50, 1.82)	1.17 (0.98, 1.39)
Agriculture, fishery, and forestry	1.30 (0.97, 1.73)	1.75 (0.76, 4.02)	1.26 (1.00, 1.58)*
Transportation	1.05 (0.75, 1.47)	1.10 (0.43, 2.80)	1.17 (0.91, 1.51)
Construction and mining	1.65 (1.21, 2.24)**	2.39 (1.20, 4.77)*	1.44 (1.16, 1.78)**
Manufacturing	1.25 (0.98, 1.60)	1.36 (0.70, 2.62)	1.24 (1.04, 1.49)*
Not employed	1.17 (0.91, 1.51)	0.96 (0.53, 1.72)	1.23 (1.00, 1.52)
Women	1.03 (0.78, 1.37)	0.75 (0.45, 1.24)	1.11 (1.02, 1.21)*
Age	1.03 (1.02, 1.04)***	1.06 (1.05, 1.08)***	1.05 (1.05, 1.05)***
Year of diagnosis	0.99 (0.97, 1.02)	0.97 (0.90, 1.04)	0.99 (0.97, 1.00)
Late stage	2.26 (0.84, 6.04)	2.94 (1.89, 4.58)***	2.53 (1.67, 3.84)***
Non-urothelial carcinoma	1.97 (1.46, 2.66)***	1.55 (0.90, 2.69)	1.61 (1.41, 1.84)***
High-grade	1.61 (1.21, 2.16)**	1.58 (1.00, 2.50)	1.35 (1.18, 1.54)***
Any surgery	0.42 (0.30, 0.59)***	0.61 (0.38, 0.97)*	0.81 (0.69, 0.95)*
Ever smoker	1.03 (0.72, 1.47)	1.09 (0.78, 1.51)	1.02 (0.92, 1.13)

[a]Missing data for stage, pathological type and grade, surgery, and smoking were multiply imputed.

[b]Missing data for occupation, stage, pathological type and grade, surgery, and smoking were multiply imputed.

*$P < .05$.

**$P < .01$.

***$P < .001$.

features and smoking habits) have been thought to underlie occupational disparities in bladder cancer survival in previous studies,[8,9] the occupational disparity remained significant even after controlling for relevant prognostic factors in the current study. Therefore, other pathways not included in conventional clinicopathological prognostic factors may have played a role.

For example, physically active patients tend to have better cancer prognosis for cancers of the breast, colorectum, and prostate compared with their sedentary counterparts.[19] Although the benefits of active lifestyle have not been documented on bladder cancer survival, sedentary lifestyle behaviors and overweight/obesity were associated with bladder cancer risk and overweight/obesity was associated with increased risk of cancer recurrence and progression.[19-22] In Japan, the highest level of leisure-time physical activity tends to be observed in clerical workers, while the lowest level tends to be observed in white-collar workers (including professional and managerial workers) and blue-collar workers (including construction and manufacturing workers).[23]

Workplace environmental factors may partly explain the poorer prognosis in blue-collar occupations, particularly in construction and mining workers. Workers in construction and mining industries are likely to be exposed to dusty air and chemical hazards, and as a result may experience worse prognosis for not only bladder cancer but also major cancer sites, including lung, stomach, and colorectal cancers.[10,12] In the current study, each patient's longest-held occupation was used as an indicator of socioeconomic status, and was not designed to capture specific occupational/environment exposure to carcinogens. However, construction and mining workers had the poorest survival in bladder cancer, which is consistent with previous findings.[10]

Psychological pathways, including job stress, may also partly explain our results. Poor mental health conditions are associated with worse bladder cancer prognosis,[24] and high job stress tended to be seen among not only blue-collar workers but also white-collar workers in Japan, which contrasts with the pattern seen in Western countries.[13,18,25] Chronic job stress may trigger systemic inflammation and stimulate

the immune system, which is reflected by increased levels of white blood cell counts.[26] Besides, neutrophil-to-lymphocyte ratio in differential leukocyte counts is a biomarker of systematic inflammation response, and systematic reviews and meta-analyses suggest that a poorer bladder cancer prognosis is associated with higher levels of neutrophil-to-lymphocyte ratio.[27-30] Therefore, as seen in recent studies for other cancer mortalities in Japan,[11,12] it is plausible that bladder cancer patients in blue-collar and the highest class occupations (ie, professionals and managers) might have a worse prognosis compared with clerical workers.

A further potential behavioral mechanism for occupational disparities in bladder cancer survival is timely receipt of treatment, a key factor in bladder cancer prognosis. Japan introduced a universal health care system in 1961, and access to bladder cancer treatment is available to patients irrespective of their socioeconomic status, which should have flattened the occupational gradient in bladder cancer survival.[31] However, as suggested previously, socially disadvantaged groups may have a higher likelihood of delaying the initiation of treatment, which may result in poor prognosis in that group.[32]

Additionally, the occupational disparities in smoking behavior could partly explain the residual disparities in bladder cancer survival. In Japan, higher occupational class workers tend to smoke as much (or sometimes even more) compared with their lower occupational class counterparts, and the occupational distribution of smoking behaviors differs markedly from Western countries.[13,33] Therefore, it would be plausible that working in the highest occupational classes did not show the most favorable survival chance in the current study.

Several limitations should be noted. First, although our data set was based on a population-based cancer registry, our internal validity and external generalizability were limited due to sizable missing data. Additionally, self-employed workers (eg, own a small family business) might be potentially misclassified to a high-status occupational class (eg, managerial positions in a huge industrial company). Although the observed occupational disparities did not materially change in sensitivity analyses among different subgroups using multiple imputation, the results were based on imputed data from the 15% of bladder cancer patients registered in KCR. However, occupational distribution in KCR parallels the national statistics and previous studies in Japan.[13,14,16-18] Second, although studies suggest that occupational class is associated with educational attainment in Japan,[11] we could not assess the contribution of relevant socioeconomic indicators (ie, educational attainment and income), physical activity, obesity, job stress, neutrophil-to-lymphocyte ratio, detailed smoking behavior (status and intensity), as well as timely standardized treatments and treatment regimens.[34] Despite these limitations, although previous studies did not sufficiently assess possible known prognostic factors,[8,9] we controlled for those prognostic factors for a subset of our patients.

In conclusion, occupational disparities in bladder cancer survival appeared to exist in Japan even after controlling for known prognostic factors, suggesting occupation may be a crucial independent determinant of bladder cancer survival. However, questions remain regarding whether the major risk behavior of smoking and other potential psychological and behavioral pathways may explain the residual occupational disparities. Hence, future studies should attempt to integrate all of the clinicopathological, psychological, and behavioral aspects, in order to overcome occupation-oriented survival inequalities in this site.

CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

AUTHOR CONTRIBUTIONS

Conception and design, Masayoshi Zaitsu, Ichiro Kawachi: Development of methodology, Masayoshi Zaitsu, Ichiro Kawachi: Acquisition of data, Masayoshi Zaitsu, Takumi Takeuchi: Analysis and interpretation of data, Masayoshi Zaitsu, Hye-Eun Lee, Sangchul Lee, Takumi Takeuchi, Yasuki Kobayashi, Ichiro Kawachi: Writing, review and/or revision of the manuscript, Masayoshi Zaitsu, Hye-Eun Lee, Sangchul Lee, Takumi Takeuchi, Yasuki Kobayashi, Ichiro Kawachi: Administrative, technical, or material support, Masayoshi Zaitsu, Takumi Takeuchi, Yasuki Kobayashi, Ichiro Kawachi: Study supervision, Masayoshi Zaitsu, Takumi Takeuchi, Yasuki Kobayashi, Ichiro Kawachi.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the Kanagawa Cancer Registry (KCR). Restrictions apply to the availability of these data, which were used under license for this study by the KCR; research data used in the study cannot be made publicly available directly by the authors. If any person wishes to verify our data analysis, they are most welcome to contact the corresponding author.

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