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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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目　　　次

Ⅰ．総括研究報告
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 ------------------------ 1
研究代表者　小林 廉毅

II. 分担研究報告
膀胱がん患者における腫瘍組織の
遺伝子変異の検討 -- 39
研究分担者　武内 巧

労働者健康安全機構病職歴データベースを用いた
癌と職業の関連の検討　―産業に起因する運動量
及び化学物質曝露と癌の関連の推測― ----------------------- 47
研究分担者　佐藤 譲
研究協力者　金子 麗奈

III. 研究成果の刊行に関する一覧表 ------------------------------ 67

IV. 研究成果の刊行物・別刷 ------------------------------ 69

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I. 総括研究報告

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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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。

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 690 万件の入院患者病職歴調査データベース（病職歴データベース）である。同データベースの職業歴は、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。また、生活習慣や特殊健康診断等の受診歴等についても調べられている。そのほか、PRTR（Pollutant Release and Transfer Register：化学物質排出移動量届出制度）のデータについて、経年および地域別に集計し、特徴を記述した。

病職歴データベースを用いて、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、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ている。これらの結果についてさらに分析を進めることにより、産業・職業とがん罹患リスクに係わる要因を検討する手がかりを得ることができると考えられる。

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A. 研究目的

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、幅広い職業・産業から化学物質に対する曝露を網羅的に探索し、化学物質曝露とがん罹患のリスクの関係の状況を把握する手法は開発されていない。また、日本における各職業とがん発症リスクの関係も網羅的に評価をされていない。

本研究では、まず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、胆管がんで評価することを目的とした（研究 1）。

つぎに、幅広い職業および産業分類を、先行研究で用いた職業・産業グループに分類し（Zaitsu 2018a）、男性における職業と各種がん発症のリスクの関連を網羅的に解析することを目的とした。また、女性における職業と各種がんのリスクの関連、およびがん以外の生活習慣病として循環器疾患の発症リスクも予備的・補足的研究として解析した（研究 2）。

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（研究 3）。

B. 研究方法

（Ⅰ）研究 1 および研究 2

<u>データセッティング</u>

独立行政法人労働者健康安全機構が保有する ICOD-R データを用いて hospital-based case-control study を実施した。ICOD-R は、全国 33 か所の労災病院（2018 年 11 月時点）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 1984 年からデータベース化を行っている。2018 年までに約 690 万件のデータが蓄積されている。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、飲酒の生活習慣の項目などがある。また、2005 年からは健康診断での生活習慣病の有無（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。また、特殊健診診断（有機溶剤、鉛、特定化学物質など）を実施されたかどうかの項目も含まれている。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管理士、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。我々は、独立行政法人労働者健康安全機構との取り決めにより、匿名化されたデー

タセットを取得した。

なお、ICOD-R の詳細ついては先行研究（Zaitsu 2018a）および独立行政法人労働者健康安全機構のホームページを参照されたい（https://www.research.johas.go.jp/bs/）。

症例 case と対照 control

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（Zaitsu 2019a）。

研究 2. 各職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：化学物質への曝露および網羅的な職業分類

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有無、鉛健康診断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。今回のデータセットでは、特定化学物質健康診断を受けていた患者にがん発症を認めなかったため、化学物質への曝露については、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（Zaitsu 2018a）。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 (Zaitsu 2018a)。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、先行研究に基づき解析対象者 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（model 1）。次に追加で喫煙と飲酒を調整した OR（95% CI）も求めた（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。

（II）研究 3

資料・データ

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）別死亡数から、全国および都道府県別に算出した。

分析方法

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。

C. 研究結果

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（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（モデル 2、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（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（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（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（Zaitsu 2018b）。また、循環器疾患では、専門職や管理職従事者で冠動脈疾患のリスクが高い一方、脳血管疾患のリスクが低く、全体としてリスクが相殺されていた（Zaitsu 2019b）。

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）。

D. 考察

本研究の結果、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、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。

専門職や管理職従事者でがん罹患のリスクが低くなる原因としては、喫煙や飲酒などのリスク要因となる生活習慣の職業格差が考えられている。しかし、本研究では、喫煙や飲酒によるがん罹患リスクの職業格差を完全には説明できなかった。喫煙や飲酒以外のリスクファクターの関与、例えば食生活習慣（塩分）、幼少期のピロリ菌への感染、職業によって異なる未知なる環境要因への曝露、また受動喫煙などの可能性が推察される。その他の消化器がん（食道、肝臓、膵臓がん）でも職業格差が観察できたことから、食生活習慣（野菜やフルーツ摂取）やウイルス感染の格差などの関与も考えられる。膀胱がんや悪性リンパ腫などでも職業格差の傾向が見られたため、有機溶剤や殺虫剤などの化学物質への関与も考えられるが、研究 1 の結果と照らし合わせると、現状では化学物質の曝露が関与しているという直接的な証拠はない。現時点では、職業による特定のがん罹患リスクの格差を生じる要因については不明である。大腸がんでは職業格差は見られなかった。日本の大腸がんの罹患率は欧米と同程度の高さであるものの、専門職や管理職従事者で大腸がんのリスクが高い欧米と比べると、今回の結果は、先行研究と傾向が異なる。原因としては食習慣の違いが

可能性として挙げられる。

一方、前立腺がんについては専門職や管理職従事者でリスクが高い可能性が示唆された。これには、職場の健康診断で PSA 健診のオプションを専門職や管理職従事者がより多く選択し、過剰診断を受けている可能性が示唆される。実際に、非雇用者である「その他」のグループではオッズ比が低くなっていることからも、その可能性は高いと考えられるが、日本における前立腺がんスクリーニングに対するエビデンスが少ないことから、今後の研究の進展を待つ必要があろう。

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。しかし、フィンランドなどの北欧諸国で行われているような、より精度の高い職業センサス情報とのリンケージができていないため、今後の研究課題として挙げられる。また、肥満や食事、身体活動などのデータの評価ができていないため、これも今後の研究課題としたい。

研究 3 によれば、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，吉岡昌徳．PRTR データと環境濃度の比較による大気中揮発有機化合物の評価．兵庫県立健康環境科学研究センター紀要 2004; 1: 67-77）。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。今後、両者の関連について他の要因も含めて検討を進める予定である。

E. 結論

日本において、特殊健診受診者（有機溶剤および鉛）において、がんのリスクが上昇するということは検出できなかったものの、がん罹患リスクには職業格差が存在することが明らかとなった。

F. 健康危険情報

なし

G. 研究発表

1. 論文発表

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2. 学会発表

なし

H. 知的財産権の出願・登録

なし

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

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。

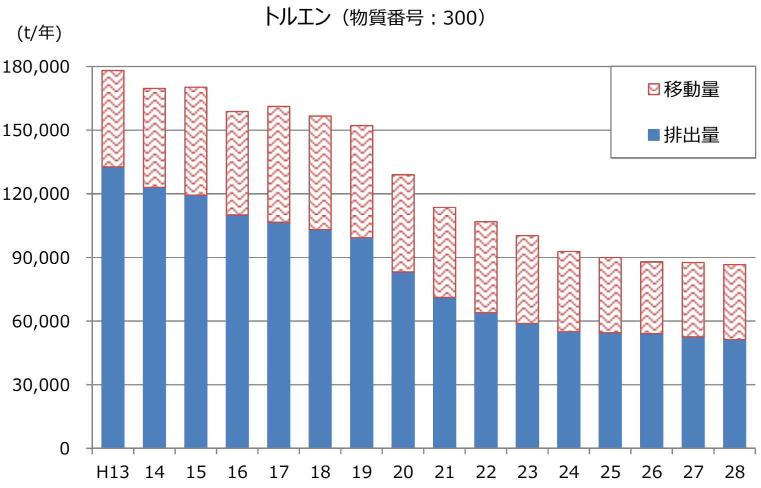


図 1. トルエンの全国排出量・移動量の推移

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。

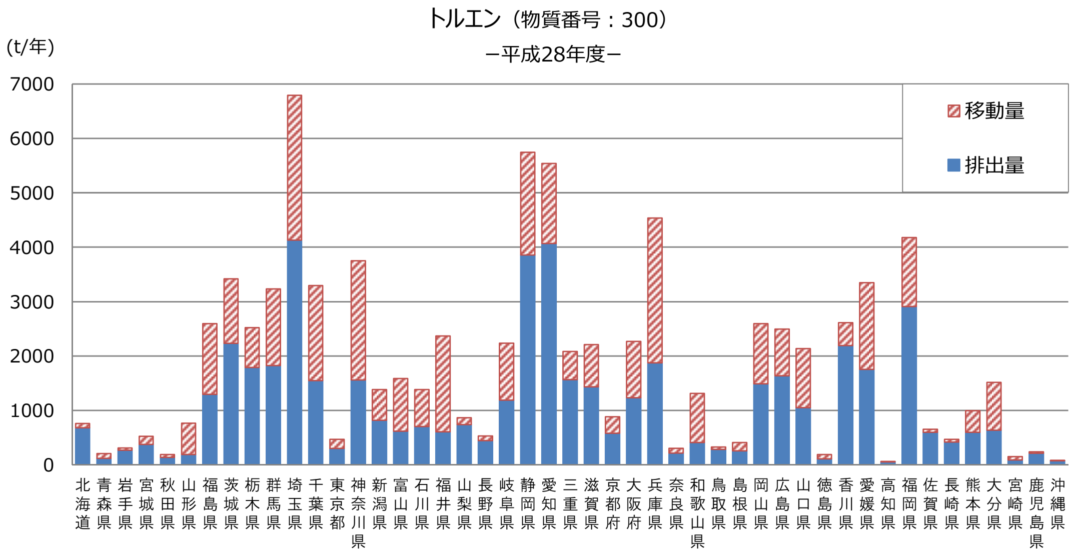


図 2. トルエンの都道府県別排出量・移動量（平成 28 年度排出分）

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。

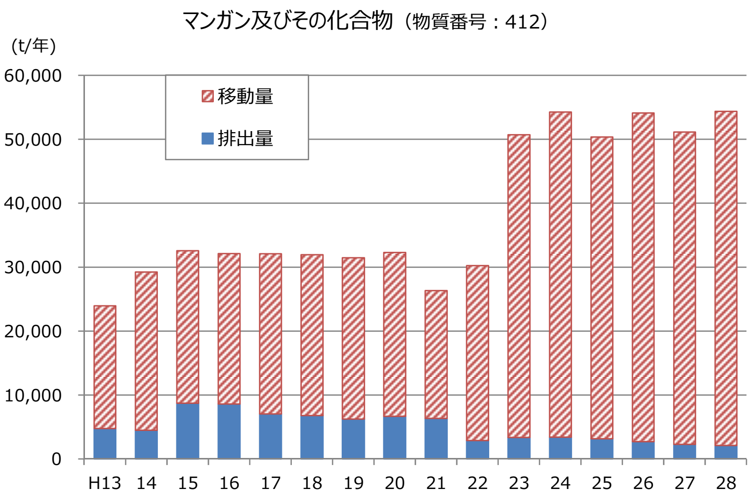


図 3. マンガン及びその化合物の全国排出量・移動量の推移

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。

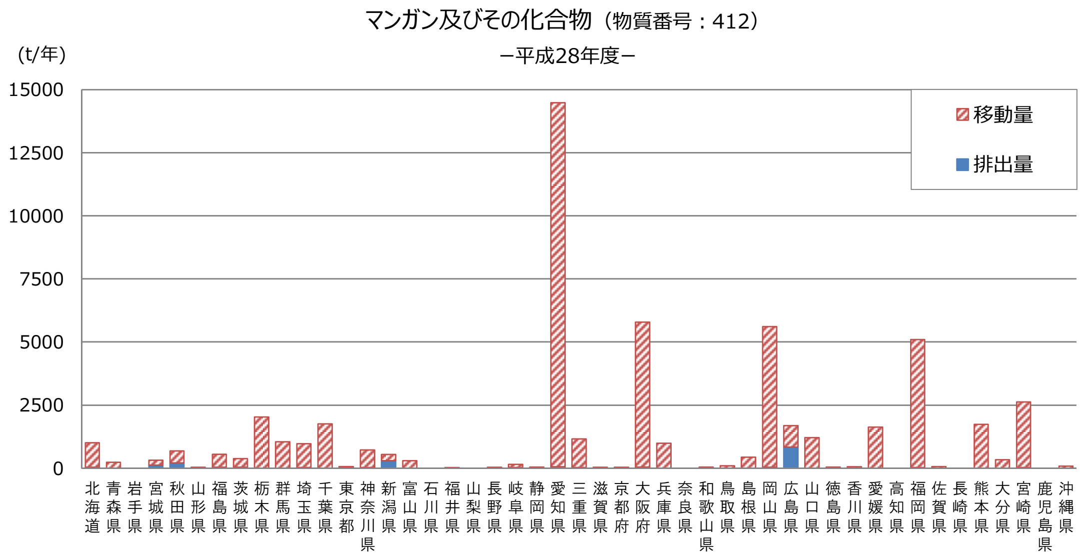


図 4. マンガン及びその化合物の都道府県別排出量・移動量（平成 28 年度排出分）

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）。

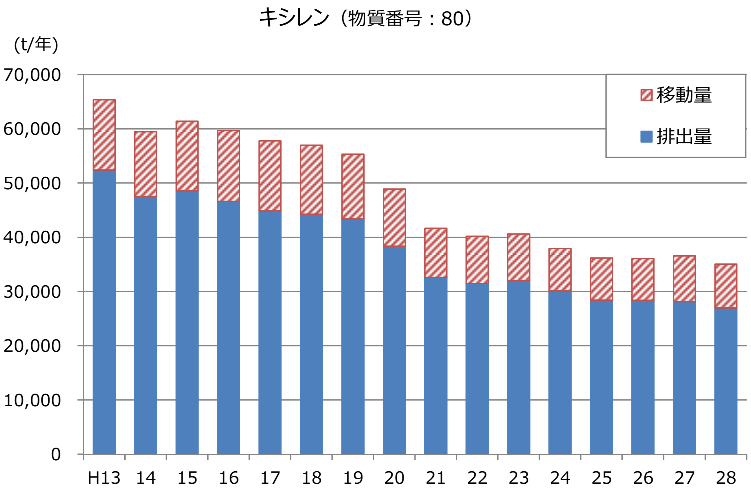


図 5. キシレンの全国排出量・移動量の推移

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。

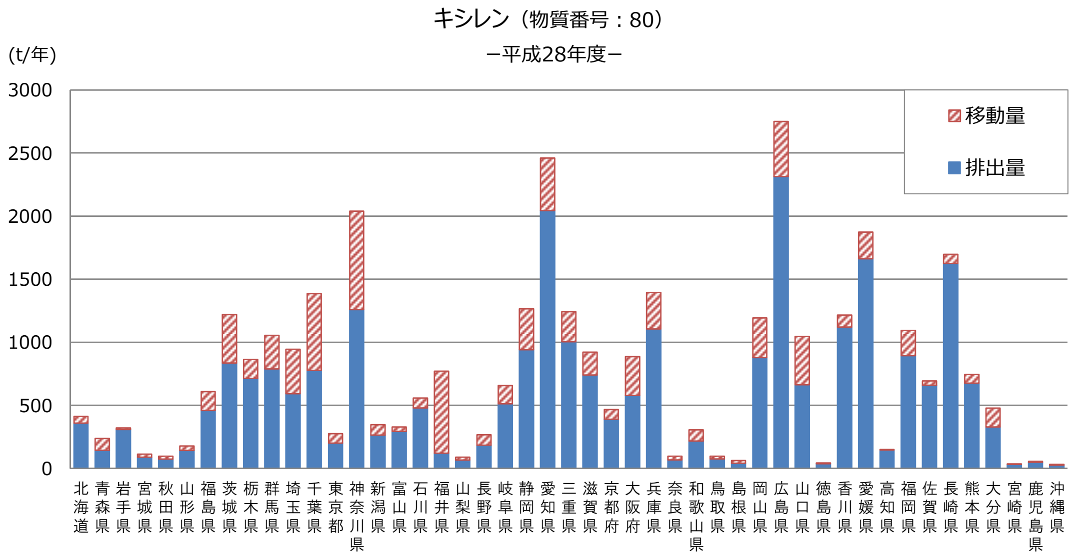


図 6. キシレンの都道府県別排出量･移動量(平成 28 年度排出分)

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)。

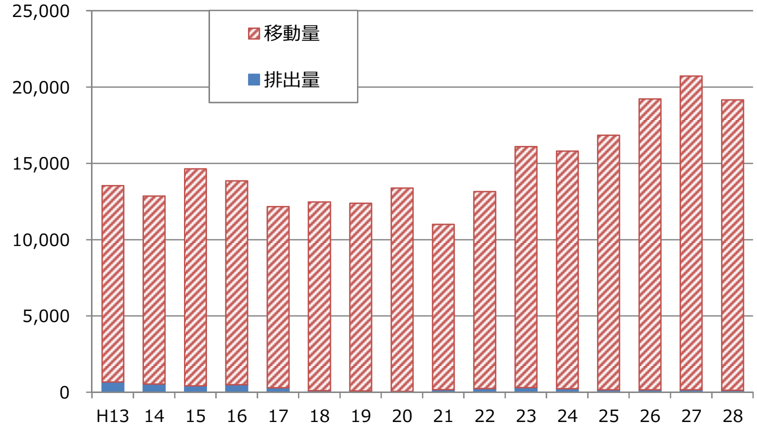


図 7. クロム及び三価クロム化合物の全国排出量・移動量の推移

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。

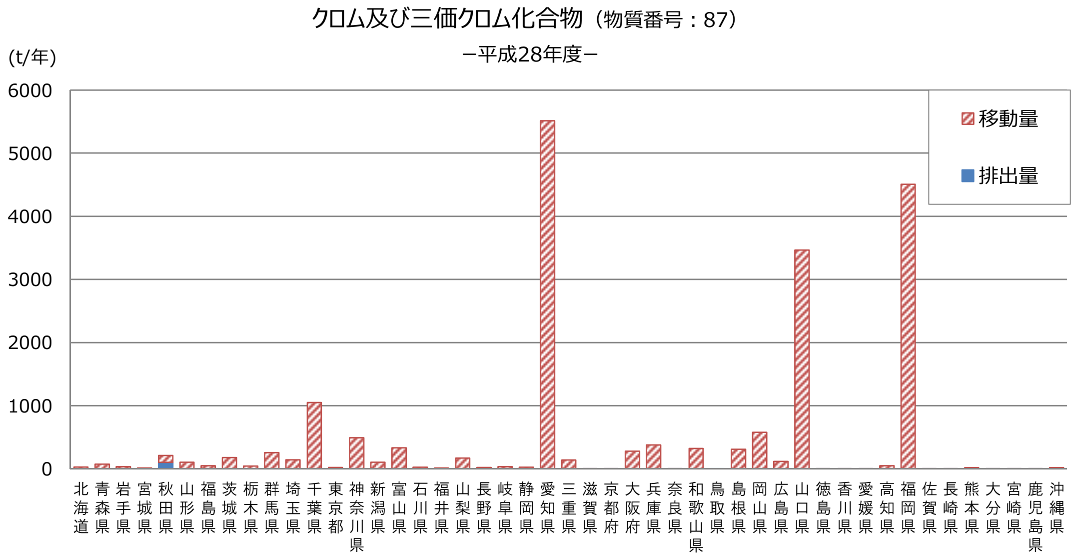


図 8. クロム及び三価クロム化合物の都道府県別排出量・移動量（平成 28 年度排出分）

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。

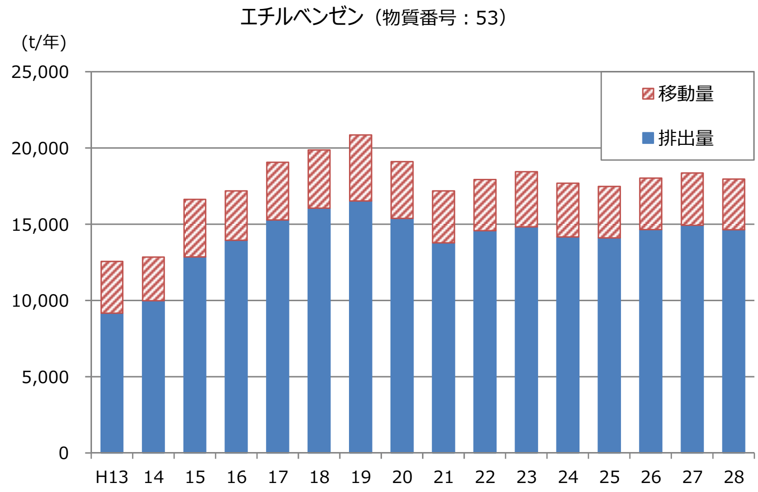


図 9. エチルベンゼンの全国排出量・移動量の推移

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。

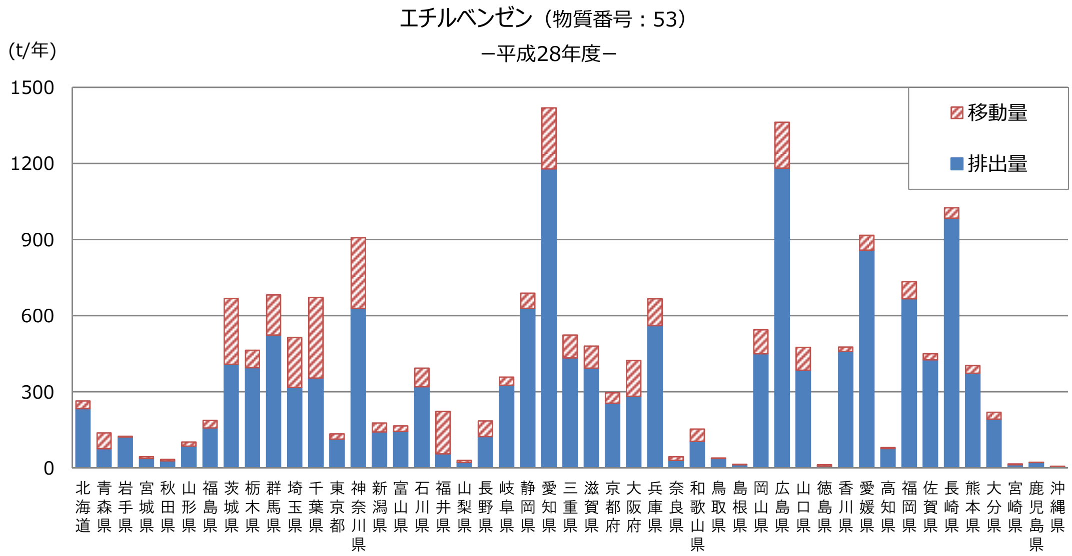


図 10. エチルベンゼンの都道府県別排出量・移動量（平成 28 年度排出分）

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。

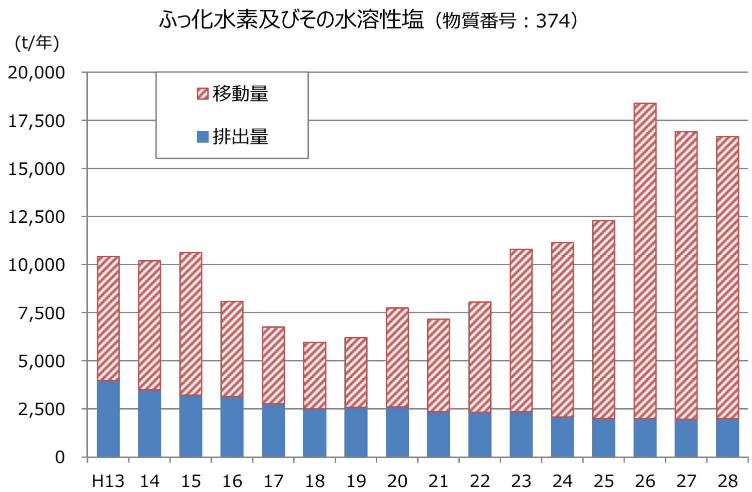


図 11. ふっ化水素及びその水溶性塩の全国排出量・移動量の推移

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。

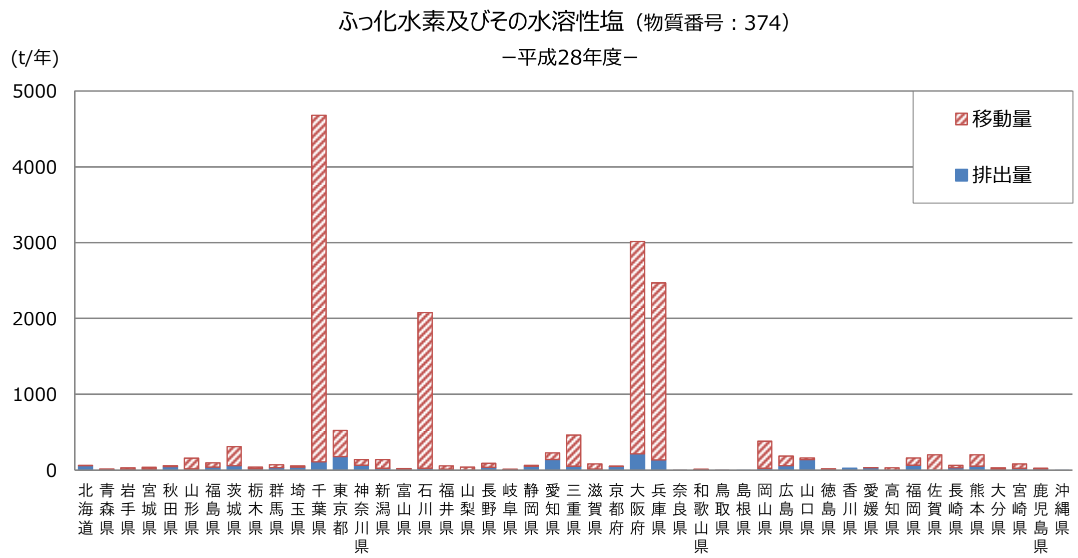


図 12. ふっ化水素及びその水溶性塩の都道府県別排出量・移動量(平成 28 年度排出分)

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。

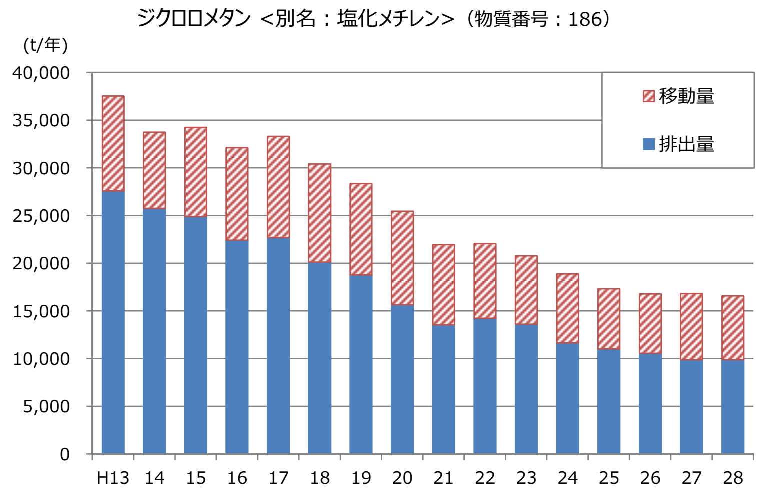


図 13. ジクロロメタン（別名：塩化メチレン）の全国排出量・移動量の推移

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。

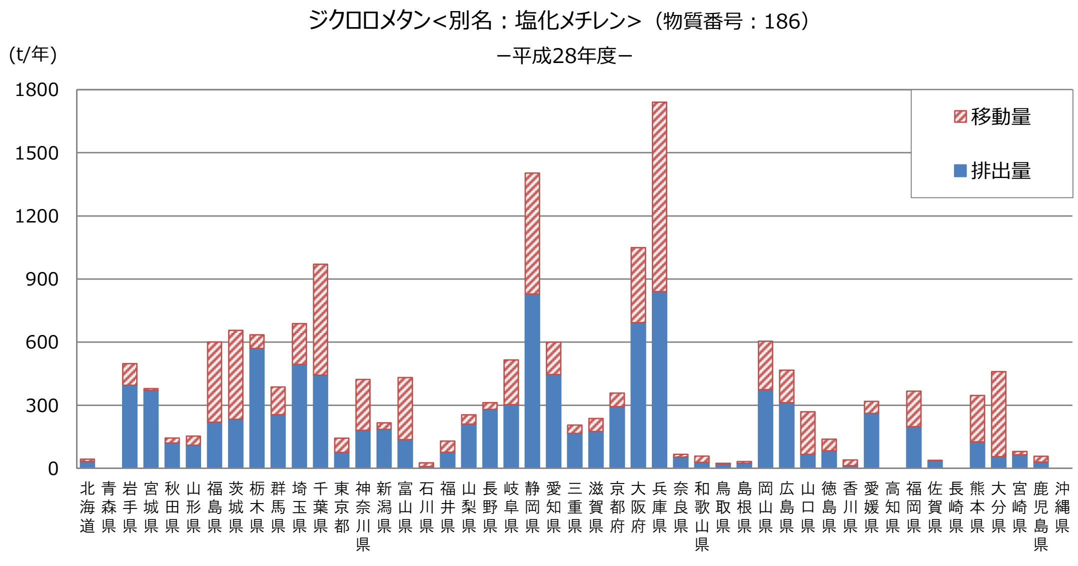


図 14. ジクロロメタン（別名：塩化メチレン）の都道府県別排出量・移動量（平成 28 年度排出分）

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。

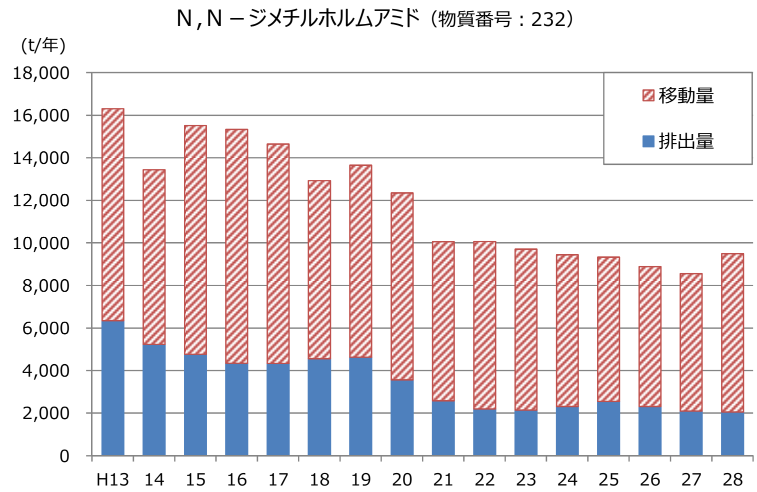


図 15. N,N-ジメチルホルムアミドの全国排出量・移動量の推移

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。

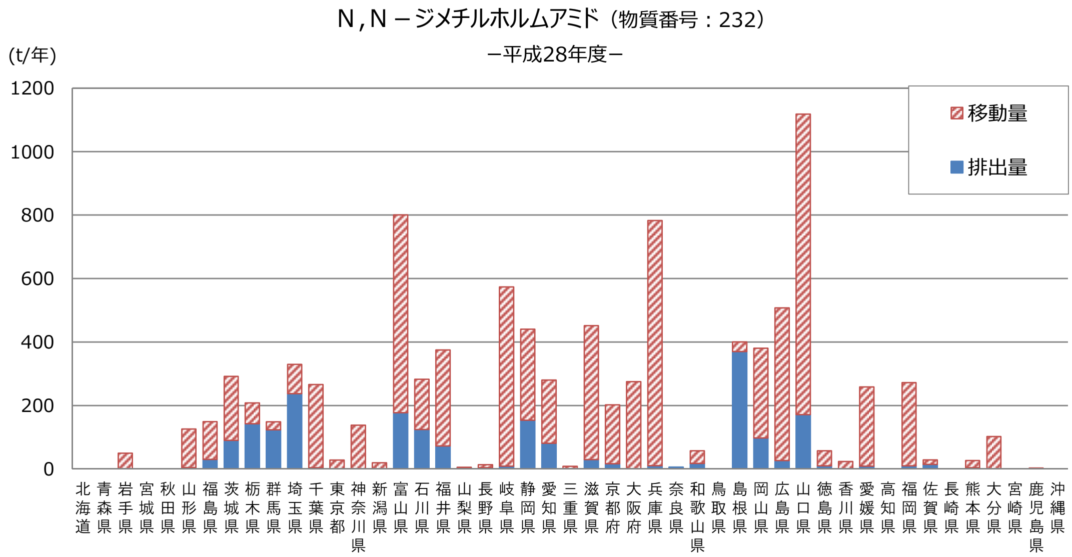


図 16. N,N-ジメチルホルムアミドの都道府県別排出量・移動量（平成 28 年度排出分）

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。

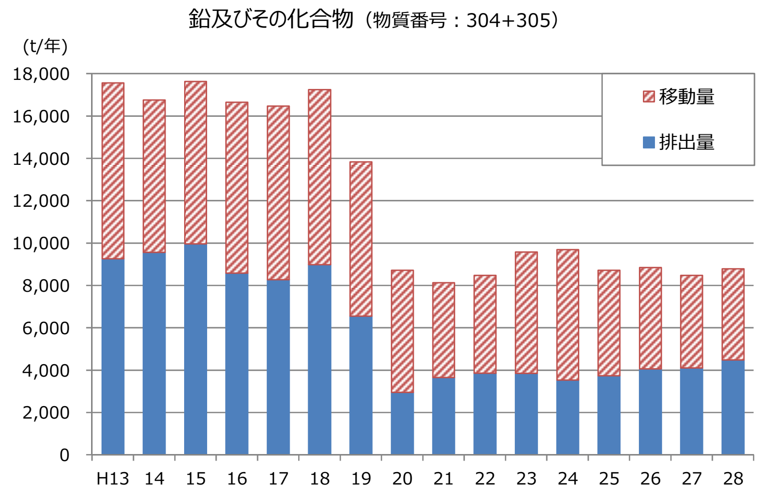


図 17. 鉛及びその化合物の全国排出量・移動量の推移

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。

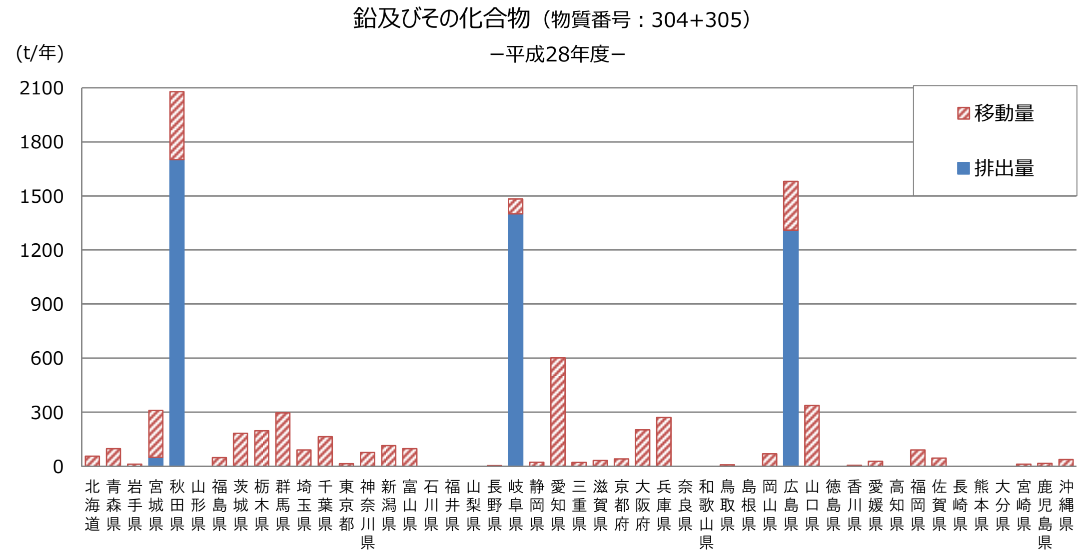


図 18. 鉛及びその化合物の都道府県別排出量・移動量（平成 28 年度排出分）

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。

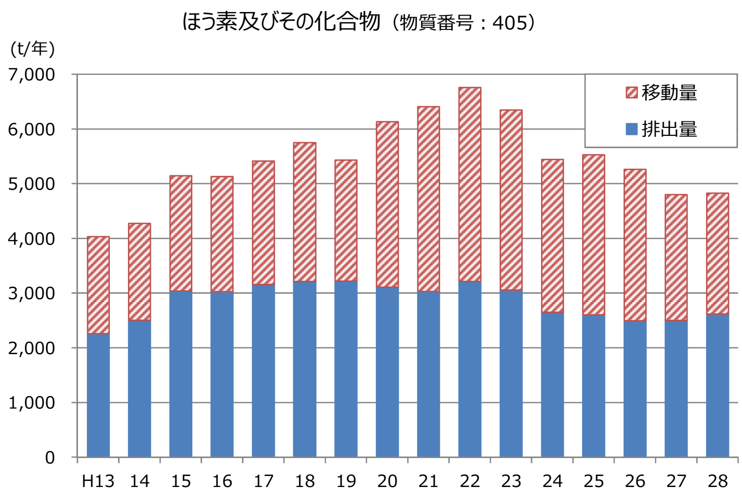


図 19. ほう素及びその化合物の全国排出量・移動量の推移

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。

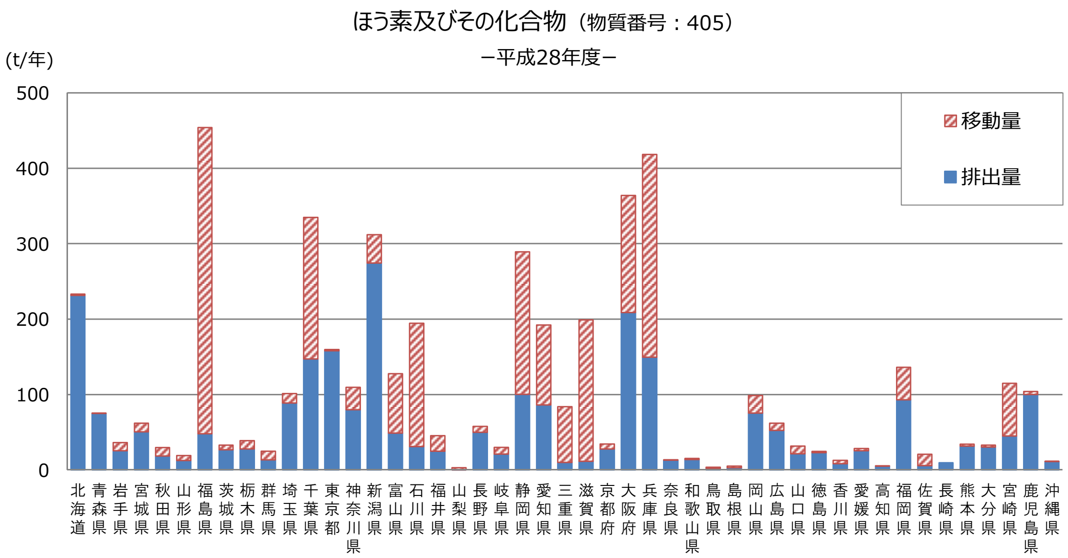


図 20. ほう素及びその化合物の都道府県別排出量・移動量（平成 28 年度排出分）

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。

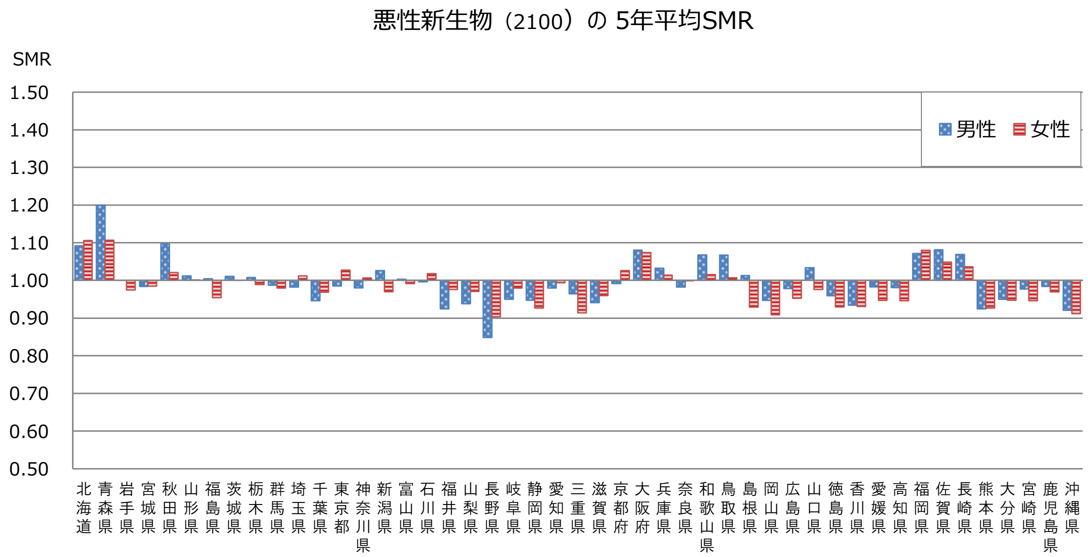


図 21. 悪性新生物による都道府県別 5 年平均 SMR(平成 23～27 年)

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。

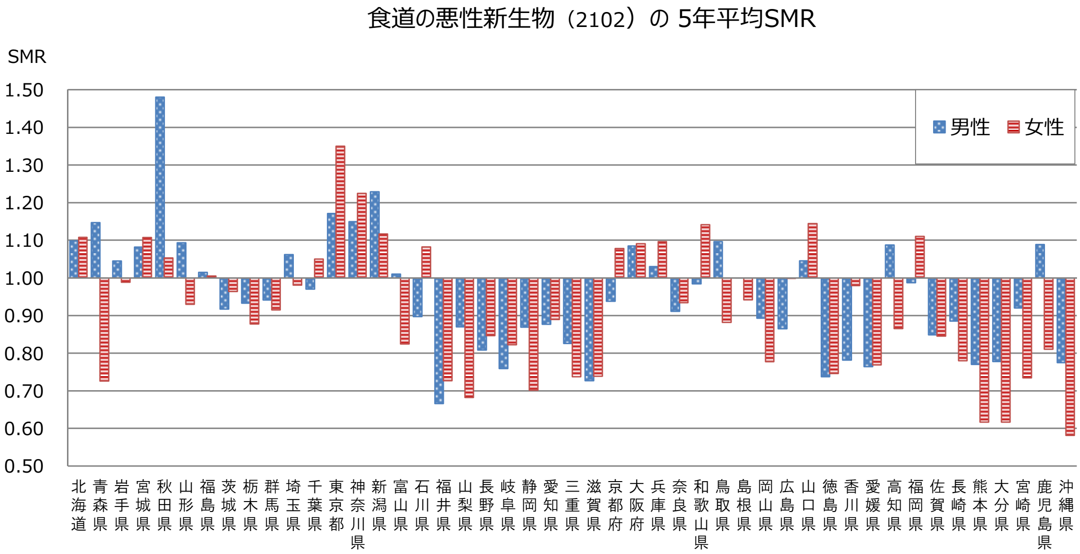


図 22. 食道の悪性新生物による都道府県別 5 年平均 SMR（平成 23～27 年）

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。

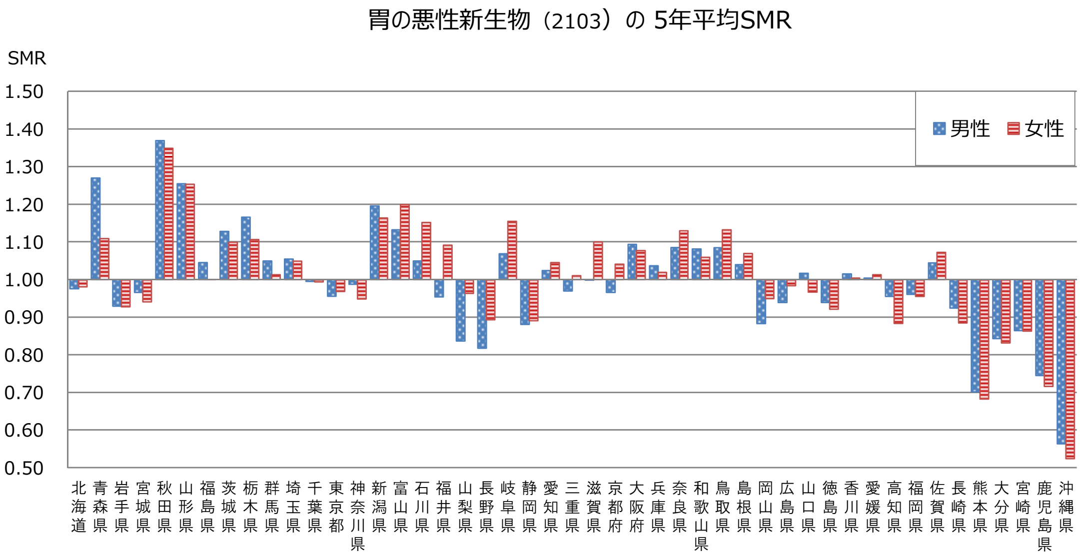


図 23. 胃の悪性新生物による都道府県別 5 年平均 SMR（平成 23～27 年）

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。

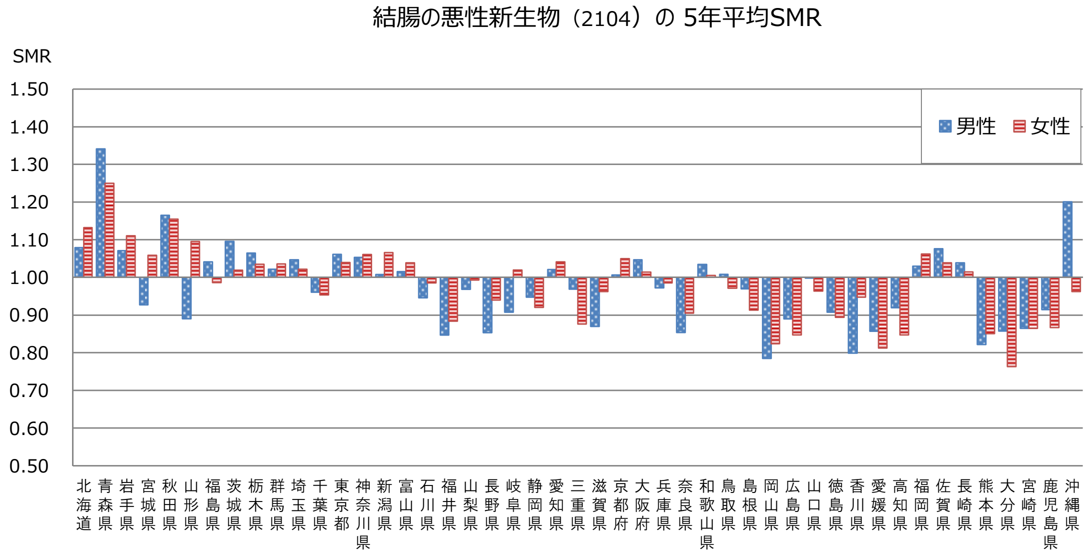


図 24. 結腸の悪性新生物による都道府県別 5 年平均 SMR（平成 23～27 年）

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）。

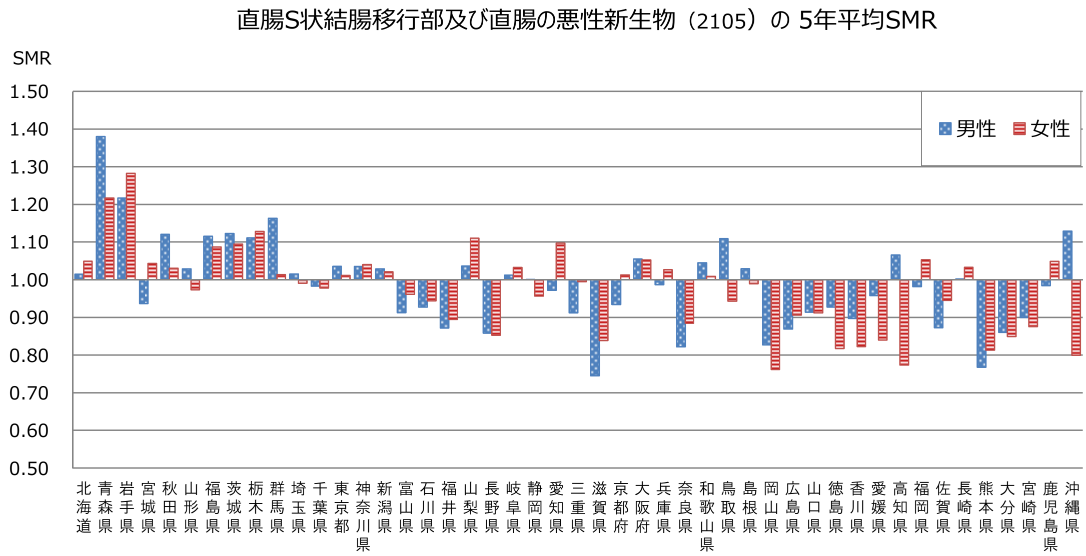


図 25. 直腸 S 状結腸移行部及び直腸の悪性新生物による都道府県別 5 年平均 SMR（平成 23～27 年）

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。

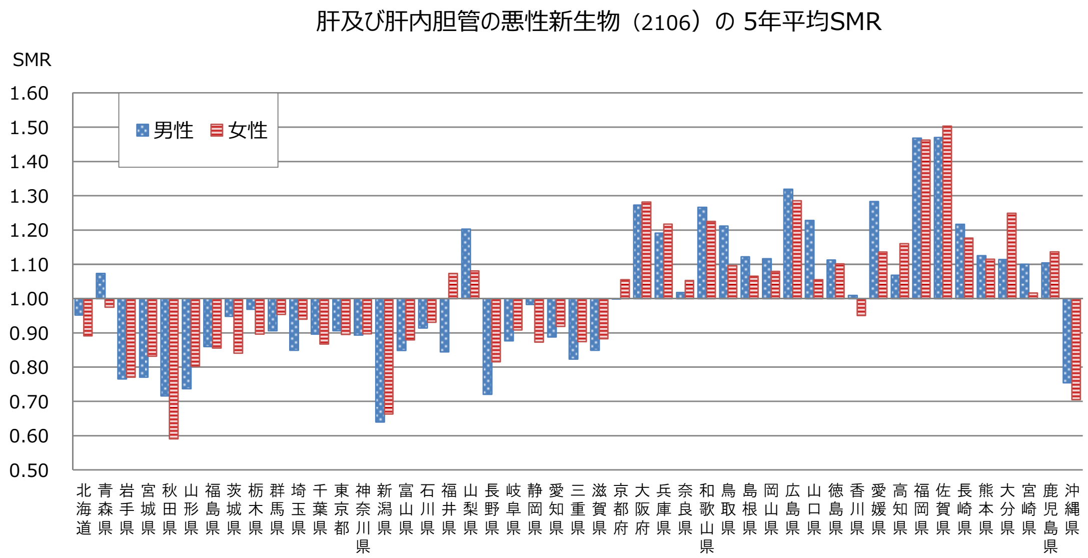


図 26. 肝及び肝内胆管の悪性新生物による都道府県別 5 年平均 SMR（平成 23～27 年）

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。

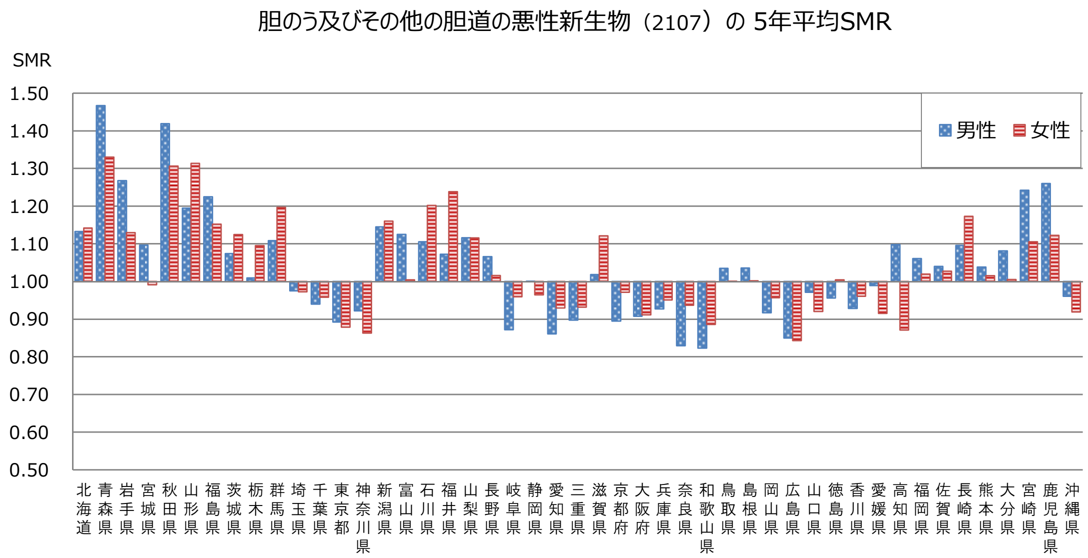


図 27. 胆のう及びその他の胆道の悪性新生物による都道府県別 5 年平均 SMR（平成 23～27 年）

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。

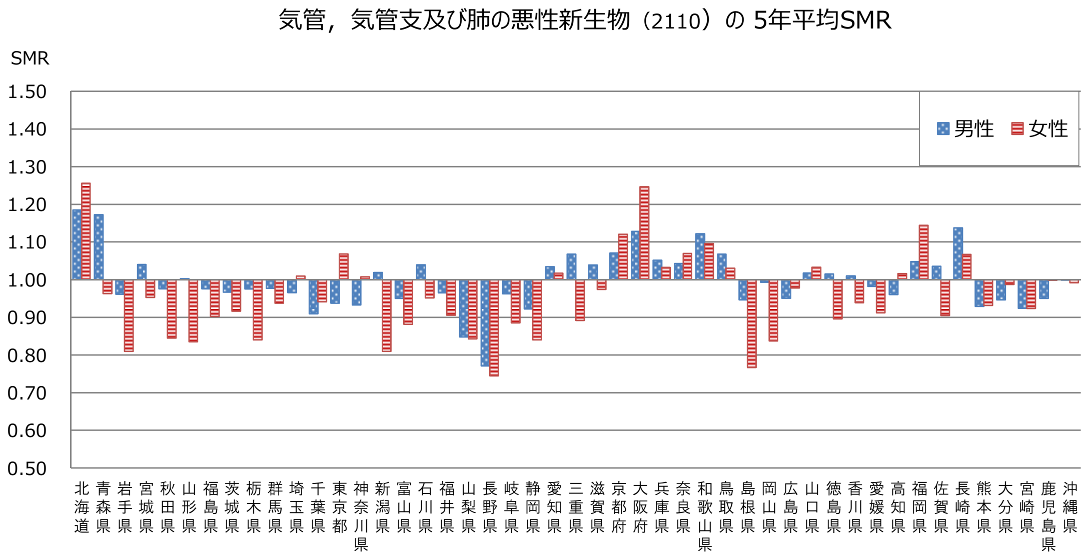


図 28. 気管，気管支及び肺の悪性新生物による都道府県別 5 年平均 SMR（平成 23～27 年）

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）。

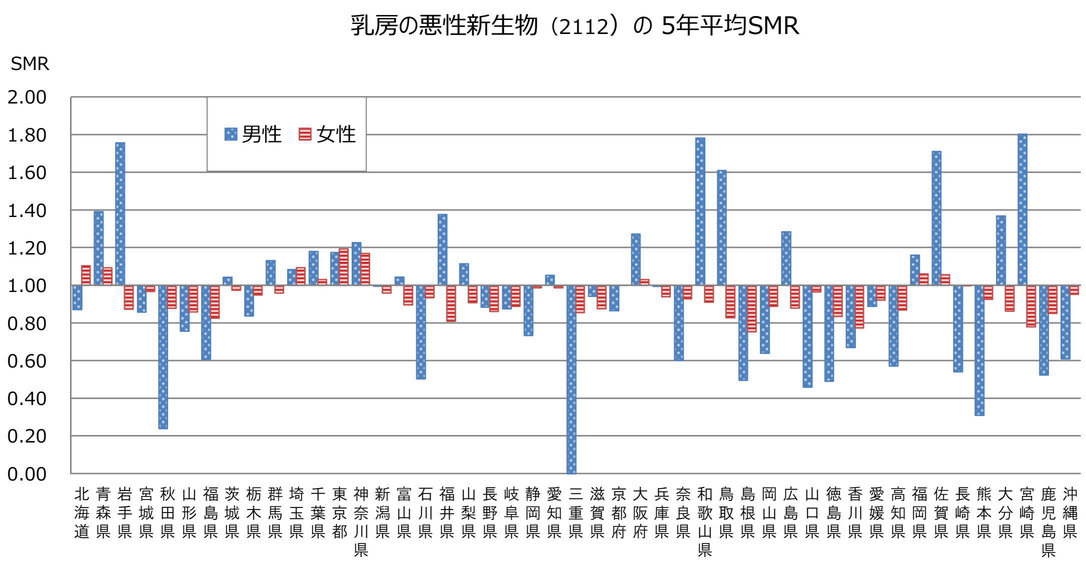


図 29. 乳房の悪性新生物による都道府県別 5 年平均 SMR（平成 23～27 年）

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。

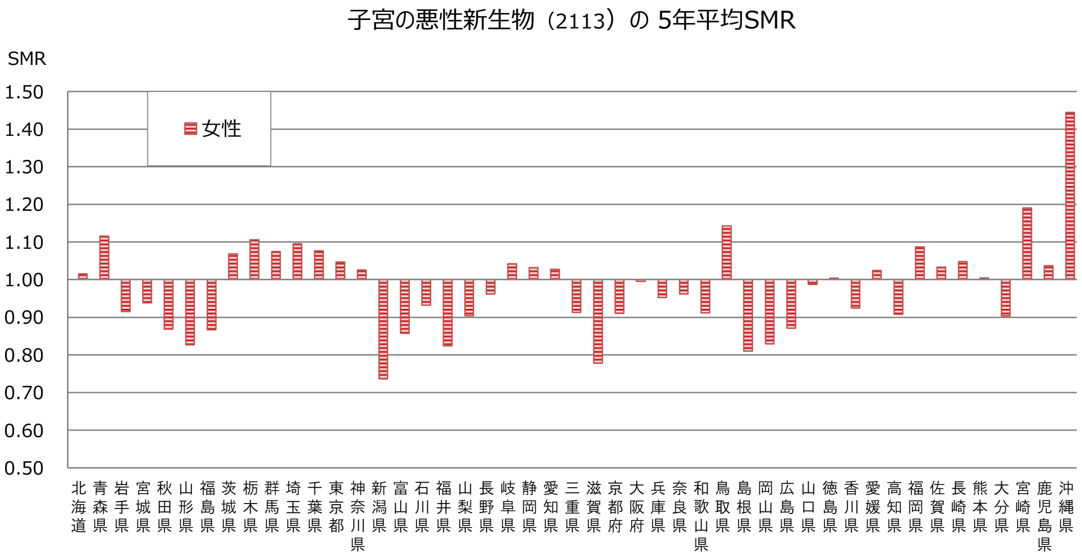


図 30. 子宮の悪性新生物による都道府県別 5 年平均 SMR(平成 23～27 年)

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。

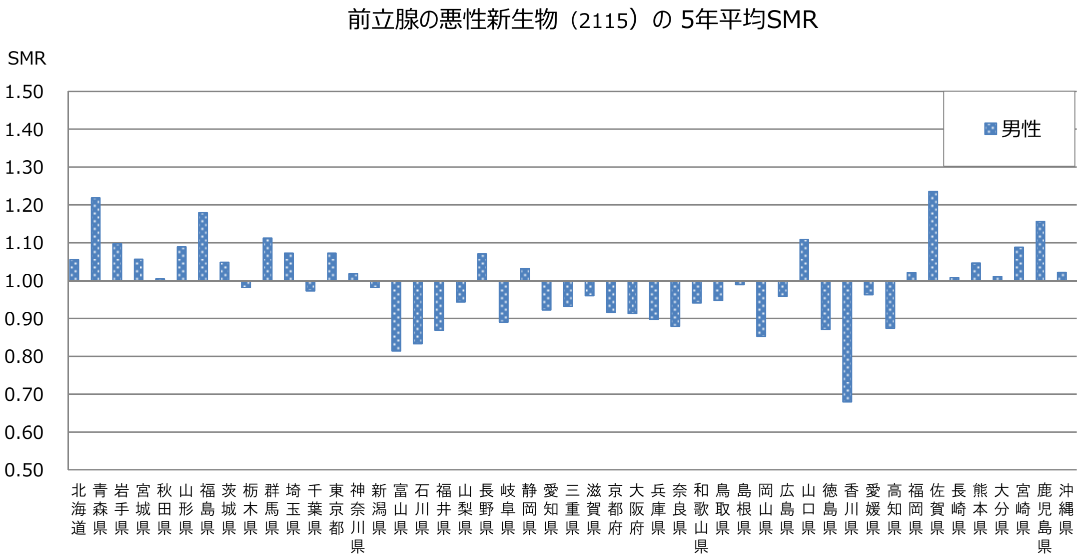


図 31. 前立腺の悪性新生物による都道府県別 5 年平均 SMR(平成 23～27 年)

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。

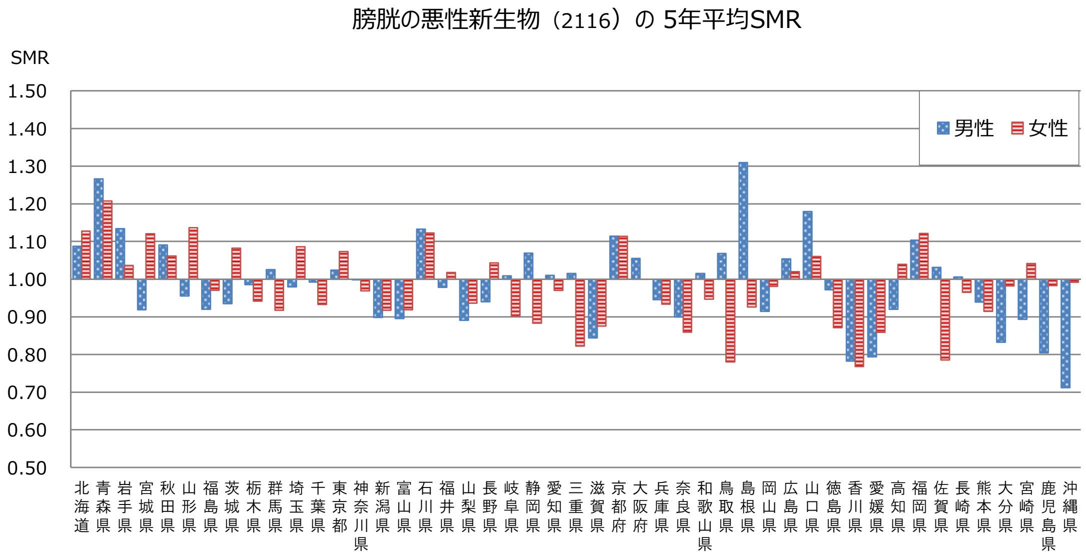


図 32. 膀胱の悪性新生物による都道府県別 5 年平均 SMR(平成 23～27 年)

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)。

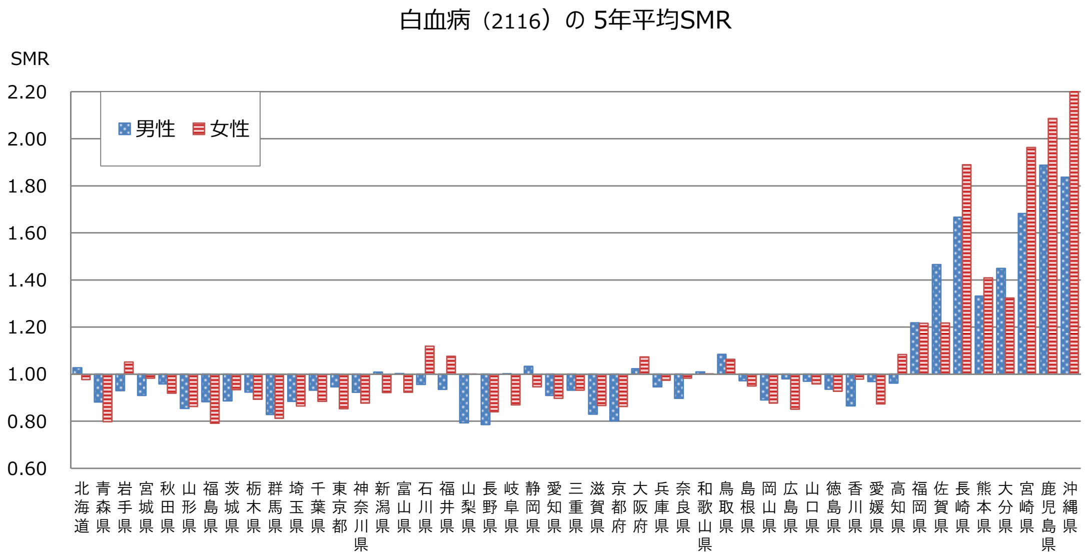


図 33. 白血病による都道府県別 5 年平均 SMR(平成 23～27 年)

II. 分担研究報告

労災疾病臨床研究事業費補助金
分担研究報告書

膀胱がん患者における腫瘍組織の遺伝子変異の検討

研究分担者　武内　巧　関東労災病院泌尿器科部長

研究要旨
（緒言）
ZNF668 遺伝子は p53 及びその負の制御因子である MDM2 を制御する核蛋白質であり、乳癌においてしばしば変異が認められる。従って乳癌抑制遺伝子の可能性も示唆されている。今回、膀胱腫瘍組織から抽出した腫瘍ゲノムにおける ZNF668 遺伝子の Exon の塩基配列を検討した。また血液白血球を増加させる顆粒球コロニー刺激因子（G-CSF）を産生する尿路上皮癌は極めて予後不良である。G-CSF 産生の成因を究明するために、G-CSF 産生腫瘍由来ゲノムについて解析した。
（方法）
関東労災病院において手術の際に腫瘍を一部採取し、ゲノムを抽出、精製した。それらのゲノムを鋳型にして ZNF668 遺伝子及び G-CSF 遺伝子の塩基配列を決定した。また尿路上皮腫瘍のパラフィン包埋標本を用いて ZNF668 蛋白および G-CSF 蛋白の発現を組織免疫染色法にて施行した。
（結果）
膀胱腫瘍ゲノムにおける ZNF668 遺伝子塩基配列解析は継続中である。膀胱癌組織における ZNF668 蛋白発現の低下は膀胱癌細胞の間質浸潤、筋層浸潤の有無と関連していた。尿路上皮癌における G-CSF 蛋白産生は癌由来ゲノムにおける G-CSF 遺伝子塩基配列の変異との関連は見られないように思われた。G-CSF 遺伝子のコピー数の相違は G-CSF 蛋白産生と関連する可能性はありうる。
（結論）
ZNF668 は膀胱癌の組織浸潤を抑制する因子である可能性がある。尿路上皮癌における G-CSF 蛋白産生の成因についてはさらなる検討を要する。

A.　研究目的

膀胱腫瘍の発生にはタバコ、アルコール飲酒、職業による化学薬品等の有害物質への曝露による環境因子と一塩基多型に代表される生殖細胞由来の遺伝性因子の双方が重要と考えられる。前者では有害な環境因子によって膀胱尿路上皮に体細胞変異が生じ、それらが蓄積して driver となることに

より膀胱腫瘍が生じる。従って膀胱腫瘍のゲノムにどのような体細胞変異が起こっているかを解析することは膀胱腫瘍の病因論的に重要である。

我々は環境因子による体細胞変異、および生殖細胞由来の遺伝性因子を検討するために、膀胱癌患者の血液ゲノムと膀胱腫瘍ゲノムの採取、保存を行っている。現在まで血液ゲノムは約 250 例、膀胱腫瘍ゲノムは約 120 例を保存している。

以前に我々は膀胱腫瘍ゲノムと同一患者の血液ゲノムの Exome 解析の比較からいくつかの体細胞遺伝子変異を同定し、その中に ZNF668 遺伝子変異が認められた(未発表データ)。ZNF668 遺伝子は p53 及びその負の制御因子である MDM2 を制御する核蛋白質であり、乳癌においてしばしば変異が認められる (Cancer Res 71: 6524, 2011)。従って乳癌抑制遺伝子の可能性も示唆されている。今回、膀胱腫瘍組織から抽出した腫瘍ゲノムにおける ZNF668 遺伝子の Exon の塩基配列を検討した。

また、血液白血球を増加させる顆粒球コロニー刺激因子 (G-CSF) を産生する尿路上皮癌は極めて予後不良であることが知られている。関東労災病院では膀胱癌 1 例、腎盂癌 1 例が G-CSF 産生腫瘍であることを確認しており、2018 年度はこの G-CSF 産生腫瘍由来ゲノムについて解析した。

B.　研究方法

<u>膀胱腫瘍ゲノムにおける ZNF668 遺伝子解析</u>

関東労災病院において経尿道的膀胱腫瘍切除術の際に cold punch にて腫瘍を一部採取し、ゲノムを抽出、精製した。それらのゲノムを鋳型にして ZNF668 遺伝子の Exon1, 2, 3 の近傍の intron 配列より作製したプライマーを用い、PCR 法にて Exon1, 2, 3 を増幅した。更にそれらの PCR プライマーを用いてダイレクトシークエンシング法にて Exon1, 2, 3 の塩基配列を決定した。使用したプライマーは表 1 に示す。

<u>膀胱腫瘍組織における ZNF668 蛋白発現解析</u>

関東労災病院において経尿道的膀胱腫瘍切除術を施行した膀胱腫瘍のパラフィン包埋標本を用いて ZNF668 蛋白の発現を組織免疫法にて施行した。ZNF668 組織染色の解析は immunoreactive score (IRS; https://www.nature.com/articles/srep22814/tables/3)に従って 12 段階で行う。つまり染色の強さと染色される (癌) 細胞の割合を半定量的に強度[0-3]と割合[0-4]の両因子を別々に判定する。

<u>腫瘍組織における G-CSF 蛋白発現の解析</u>

G-CSF 産生腫瘍組織とコントロールの G-CSF 非産生腫瘍組織に対し、G-CSF 抗体 (Santa Cruz Biotechnology, sc-53292) を用いた組織免疫染色を施行した。

<u>G-CSF 遺伝子の解析</u>

G-CSF 産生腫瘍 2 症例とコントロールの G-CSF 非産生腫瘍 3 症例に対し解析を施行した。患者血液ゲノムと尿路上皮癌組織ゲノムにおいて G-CSF 遺伝子全体を PCR 法にて 3 部分に分けて増幅し、更にそれらの増幅産物をダイレクトシークエンシング法にて塩基配列を決定した。使用したプライマーは表 2 に示す。PCR1 は GCSF1 と GCSF2 プライマー、PCR2 は GCSF3 と GCSF4 プライマー、PCR3 は GCSF5 と GCSF6 プライマーで増幅した。

また上記の症例の患者血液ゲノムと尿路

上皮癌組織ゲノムに対し、G-CSF 遺伝子のコピー数をデジタル PCR 法で理研ジェネシス社に委託して施行した。

（倫理面への配慮）
本研究に関係する全ての研究者はヘルシンキ宣言および「人を対象とする医学系研究に関する倫理指針（平成 26 年 12 月 22 日文部科学省・厚生労働省告示第 3 号)、「ヒトゲノム・遺伝子解析研究に関する倫理指針（平成 25 年文部科学省・厚生労働省・経済産業省告示第 1 号、平成 26 年 11 月 25 日一部改正)」に従って本研究を実施する。また本研究は関東労災病院研究倫理委員会において承認された。

C.　研究結果

膀胱腫瘍ゲノムにおける ZNF668 遺伝子解析

未だ解析は進行中であるが、2018 年度は解析症例数の増加を行った。

膀胱腫瘍組織における ZNF668 蛋白発現解析

2018 年度は 48 例の検体において詳細な検討を行った。IRS と膀胱癌組織における癌細胞の間質および筋層浸潤との関連を検討した。表 3 に示すように、ZNF668 発現の低下は膀胱癌の間質浸潤、筋層浸潤と関連していた。統計解析は Welch t 検定で行った。

腫瘍組織における G-CSF 蛋白発現の解析

図 1 に示すように G-CSF 産生腫瘍では尿路上皮癌における G-CSF の発現が見られたが、G-CSF 非産生腫瘍では認めなかった。

G-CSF 遺伝子塩基配列の解析

解析結果の詳細な評価は未だ検討中であるが、G-CSF 産生腫瘍症例、G-CSF 非産生腫瘍症例共に、血液、腫瘍ゲノム間で明らかな G-CSF 遺伝子の塩基配列の違いはないように思われた。

G-CSF 遺伝子コピー数の解析

解析結果の詳細な評価は未だ検討中であるが、血液、腫瘍ゲノム間で G-CSF 遺伝子のコピー数の相違がある症例が存在する可能性をうかがわせる結果も示された。

D.　考察

膀胱腫瘍ゲノムに検出された ZNF668 遺伝子の変異が膀胱癌に発生した体細胞変異であるのか、あるいは生殖細胞ゲノムにも認められる変異であるかは正常組織においても ZNF668 遺伝子の変異の有無を検討する必要がある。このために、現在、膀胱癌患者の血液ゲノムを用いて同様の ZNF668 遺伝子解析を行い、膀胱腫瘍ゲノムとの比較を施行することを検討している。

膀胱腫瘍組織における ZNF668 蛋白発現は浸潤度の高い癌で有意に発現が低下していた。このことは ZNF668 が膀胱癌抑制遺伝子として作用している可能性に矛盾しない。

G-CSF 産生尿路上皮癌における G-CSF 産生の成因については未だ結論は出ていない。癌における G-CSF 遺伝子の塩基配列変異については血液との差異は現在まではっきりとは認めておらず、G-CSF 産生とは考えにくい。G-CSF 遺伝子コピー数の変化は G-CSF 産生の原因である可能性も示唆されているが、今後のさらなる慎重な検討が必要である。

E.　結論

膀胱腫瘍ゲノムには ZNF668 遺伝子変異が見られる可能性がある。また細胞核における ZNF668 蛋白は、浸潤度の高い膀胱癌細胞で発現が低下していた。G-CSF 産生腫瘍の成因についてはさらなる検討を要する。

F. 健康危険情報
総括研究報告書に記載

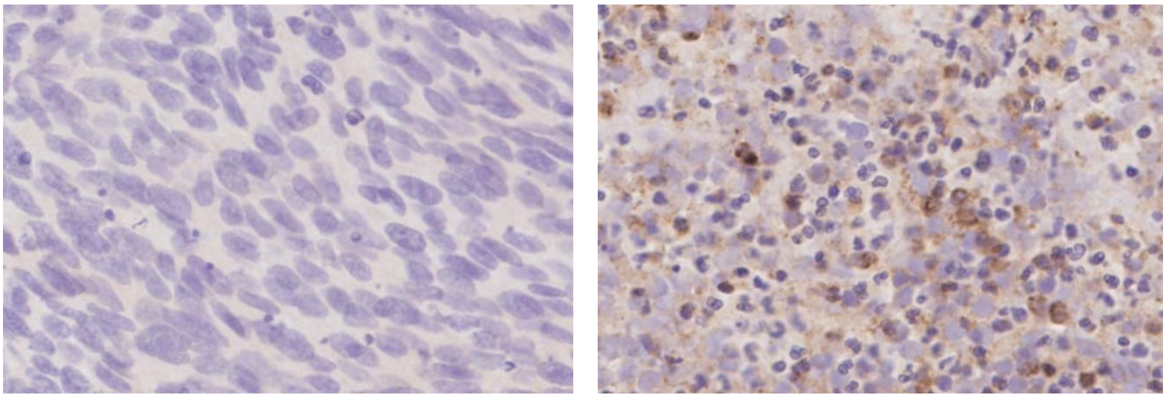
G. 研究発表

１．論文発表
なし。

２．学会発表
なし。

H. 知的財産権の出願・登録状況
なし。

図 1：膀胱癌の G-CSF 組織染色



GCSF 非産生腫瘍　　GCSF 産生腫瘍

表１：ZNF668 遺伝子の増幅に用いたプライマー

ZNF_Ex1_S: 5'-GTCCTTAGGTGCAAAAGCTTCCCCG-3'
ZNF_Ex1_AS: 5'-CCGCAGGGAAACTGAGGCCAGCTC-3'
ZNF_Ex2_S: 5'-TGAGGCTTTCAGGAGTGGCGAAGGT-3'
ZNF_Ex2_AS: 5'-TTACCCTGAGACTCAAACCCAGGCC-3'
ZNF_Ex3_S: 5'-GCAGTGGGGTCACGTTATGGGTCTG-3'
ZNF_Ex3_AS: 5'-TGATGCCCAAACTCCCACCCATTCA-3'

表 2 : G-SCF 遺伝子の増幅に用いたプライマー

GCSF1: 5'- TCGAGACCAGCCTGACCACCAACATGG -3'
GCSF2: 5'- CTGGGCCAAGACACTCACCCATCAGCT -3'
GCSF3: 5'- GGGCAAGGCGACGTCAAAGGAGGATCA 3'
GCSF4: 5'- CCCGAGGCCACCCAGAAAAACAGGAGA -3'
GCSF5: 5'- CCAGGCCTCTGTGTCCTTCCCTGCATT -3'
GCSF6: 5'- GGAAAGCAGCTTCCCTTCCTTGGAGCC -3'

表 3 : 膀胱癌組織における ZNF668 蛋白発現と腫瘍浸潤の関連

	間質浸潤なし	間質浸潤あり	p 値
IRS	7.1±3.4	4.9±1.6	p=0.004
	筋層浸潤なし	筋層浸潤あり	
IRS	6.7±3.1	4.0±1.2	p=0.001

労災疾病臨床研究事業費補助金

分担研究報告書

労働者健康安全機構病職歴データベースを用いた癌と職業の関連の検討
―産業に起因する運動量及び化学物質曝露と癌の関連の推測―

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研究要旨

これまで、職業性曝露による疾病対策は、常に重篤な有害事象が発生してから研究され、事後的に法規制が行われてきた。職業性疾病の罹患には極めて長い年月を必要とすることが多く、また医療者の関心の少ないことから職業と疾病が関連づけられないことも多く、発覚の契機は極めて少ない。職業性曝露による疾病の予防は、超長寿を可能にした医療の中でも成果の得難い研究分野といえる。そこで、本研究は、近年利用の幅が広まるビッグデータを用いて、職業がもたらす新たな癌のリスク及びその原因となるハザードの可能性について検索することを目的とした。

（１）（独）労働者健康安全機構の入院患者病職歴データベース（ICOD-R）を用い、各産業の各種癌に対するリスクを男女別に算出した。職業由来の運動の強度によって癌のリスクは変化した。多因子を調整した後、男性では、運動強度の高い産業群で各種癌に対するオッズ比が 0.61-0.79（前立腺癌、尿管癌、膀胱癌、食道癌、肝臓癌、膵臓癌、大腸癌、肺癌、乳癌）と他の職種より低く、運動強度の低い産業群で 1.09−1.44(精巣癌、膀胱癌、大腸癌)と有意に高かった。女性では乳癌のみ同様の傾向を認めた。

（２）ICOD-R より、化学物質曝露機会の多い製造業に限定し、各種癌に対する産業リスクを算出した。オッズ比が 2.0 以上となったものは、出版・印刷・同関連産業の腎盂尿管癌 2.01(95%CI 1.15-3.52)、ゴム製品製造業の腎盂尿管癌 2.82(95%CI 1.19-6.70)、なめし革・同製品・毛皮製造業で肝臓癌 2.36(95%CI 1.15-4.83)、膵臓癌 2.85(95%CI 1.26-6.47)、肺癌 2.00(1.01-3.99)、電気機械器具製造業の腎臓癌 2.49(95%CI 1.75-3.55)、腎盂尿管癌 2.09(95%CI 1.18-3.70)、情報通信機械器具製造業の腎臓癌 2.69(95%CI 1.77-4.11)、腎盂尿管癌 2.14(95%CI 1.02-4.45)、電子部品・デバイス製造業の腎臓癌 2.07(95%CI 1.37-3.13)であり、産業と癌種に傾向が見られたが、生活習慣等の交絡要因の検討が今後の課題である。なお、これらの癌症例については個々の病歴サマリを検討し、組織学的診断根拠の確認を行った。

本研究で、従事する産業が癌のリスクの一つとなりうる可能性が示唆された。また、ビッグデータから得られた稀な症例の集積性の情報について、ミクロデータに遡り、具体的に疾病の状況を確認することで、信頼性の高い新たな知見を得られる可能性が示唆された。

A. 研究目的

ジクロロメタン、ジクロロプロパンによる胆管癌、オルトトルイジンによる膀胱癌など、職業上扱う化学物質由来の発癌の報告を考慮すると、未知の職業関連疾病が数多く存在することが伺われる。長期にわたる化学物質の曝露を誘因とする発癌は、単一事業場での集団発生など、集積性を契機として見つかることが多く、個々が別の医療機関に受診することが多い現状では、職業集積性を捉えることは難しい。また、職業や就労状況に対する医療機関側の関心が一般に薄いことから、集積性を捉える機会を更に減少させている。

医療技術は発達し、あらゆる疾病罹患後の予後は延長した。しかし、依然として職業上の有害物質曝露規制は、重篤な有害事象が発生してから遡って検討され規制されるという順序は変わっておらず、未然に発見して防止するに至る研究成果を得ることは極めて難しい。そこで、IT 技術によりビッグデータの分析活用が可能となった現在、職業・就労状況に関する情報が集積されたビッグデータを用い、職業毎の疾病の集積性を算出することで、職業別のリスクを推定し、要因たるハザードの推定を行うこととした。

使用したデータは、(独) 労働者健康安全機構の全国労災病院による入院患者病職歴データベース Inpatient Clinico-Occupational Database of the Rosai Hospital Group (ICOD-R) を用いた。

① ICOD-Rを用いた癌に対する産業リスクの検討

本邦では長いこと、長時間の労働が美徳とされ評価されてきた経緯があり、就労上の作業環境や作業態様が生涯の癌リスクへ影響していることが予測される。そこで、ICOD-R を用い、癌に対する産業別のリスクと、多くの発癌に関与することが研究されている運動量について、産業ごとの運動強度を加味したリスクの評価をすることを目的とした。

② 各種製造業従事者に対する癌リスクの検討

職業上の有害化学物質曝露による癌の罹患は新たな報告は絶えない。特に製造業では有害化学物質曝露の機会が多く、防護策が必要とされる。

産業ごとの有害化学物質の曝露について、経済産業省より、事業者による化学物質の排出量等の把握と届け出が義務づけられている (PRTR： Pollutant Release and Transfer Register)。排出移動量は、個人曝露を推定するものとは言えないが、曝露されやすい物質と考えることは可能である。

そこで、ICOD-R を用い、製造業に於いて各種癌リスクの検討を行い、PRTR からその誘引となる化学物質や、曝露状態について推測検討した。

B. 研究方法

① ICOD-Rを用いた産業による癌リスクの検討

ICOD-R を用い、日本産業分類に基づいた産業と、喫煙量、飲酒量、高血圧、高脂血症、糖尿病の既往歴の登録がある症例を対象とした。これらのうち、ICD-9、ICD-10 に基づいて抽出した各種癌の症例に対し、四肢の骨折

症例から、性、年齢、登録施設（病院）、入院時期をマッチさせたコントロールを 1:1 で抽出し、症例対照研究とした。産業、飲酒量、喫煙量、生活習慣病歴を用いて男女別に条件付きロジスティック回帰分析を行なった。産業については、先行文献と症例数の大きさから、卸小売業を reference として解析を行った。

また、職業による運動強度に基づき、運動量の多い産業を農業、漁業、工業及び建設業、運動量の少ない職業を金融、不動産、研究、教育、複合サービス、その他のサービス業としてまとめ、産業による運動強度と癌リスクを検討した。

② 各種製造業従事者による癌リスクの検討

ICOD-R から、製造業に該当する症例を抽出し、各種癌症例と四肢の骨折症例を対象として、性、年齢、入院時期、産業、登録施設（病院）、飲酒量、喫煙量を変数に用いてロジスティック回帰分析を行い、各製造業ごとのリスクを検討した。産業の reference 群は、最も症例数の多い食品製造業とした。

更に、産業リスクのオッズ比が 2.0 を超えた産業と癌の組み合わせに該当する症例と、症例数が少なく、高いオッズ比を呈した癌種が多いなめし皮・同製品・毛皮製造業の全癌症例について、全国労災病院から該当サマリを取り寄せることで、ビッグデータである ICOD-R から算出された結果をミクロデータと結合させ、組織学的な癌の確定診断についても確認した上で、結果の信頼性を高めることとした。

解析には STATA/MP15.0 software (Stata-Corp LP, College Station, TX)を用いた。P値は 両側検定で、$< 0.05^{*}$、$< 0.01^{**}$を統計学的有意とした。

（倫理面への配慮）

本研究は、関東労災病院研究倫理委員会（第 2017-8 号）「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、消化器病領域の病職歴、医療経済を含めた疫学的検討」、関東労災病院（第 2014-34 号）及び東京大学倫理委員会（第 10891 号）「(独)労働者健康福祉機構全国労災病院で行われたがんとその他の疾患及び神奈川県悪性新生物登録事業における消化器癌を対象とした疫学的研究」の承認を得て実施した。

本研究の対象とした ICOD-R は、入院時に患者の同意を得て収集された入院病職歴データであり、非識別加工情報として研究者が提供を受けた。研究にあたっては、労働者健康安全機構関東労災病院及び東京大学公衆衛生学教室ホームページにて研究内容及び倫理審査内容を公開し、オプトアウトの機会を設けている。

C. 研究結果

① ICOD-Rを用いた癌に対する産業リスクの検討

全登録症例は 652 万件であり、同一症例による重複入院を除き、初回入院に限ると 418 万件、そのうち職業の登録があるものは 183 万件であった。

表 1 は主な癌腫及びコントロールとした四

肢の骨折の症例数と入院時平均年齢を示している。対象症例は 57,913 例であり、前立腺3429 例、腎臓 1450 例、食道 2414 例、胃 11839 例、肝臓 2637 例、膵臓 3056 例、大腸 12470 例、肺 8548 例、乳房 5093 例であった。

表２ではケースとコントロールの飲酒、喫煙量の平均と四分位点、生活習慣病保持者の割合を示した。飲酒、喫煙量は共に建設業、輸送業で多く、生活習慣病の割合は各産業で著明な差は認められなかった。

表３と表４に男女別の各種癌の産業ごとのオッズ比を示した。

男性のうち、第一次産業では農業・林業が大腸癌で 0.50(95%C.Ｉ 0.42-0.59)から肝臓癌で 0.71(95%C.Ｉ 0.49-0.96)、漁業が前立腺癌で 0.37(95%C.Ｉ 0.24-0.56) から肺癌で 0.69(95%C.Ｉ 0.52-0.94)といずれの癌腫でも低値を示した。運動強度の高い職業では腎盂尿管癌で 0.44 (95% CI 0.26-0.74)から、大腸癌で 0.74 (95% CI 0.66-0.82)といずれの癌に於いてもリスクが低かった。

一方、女性では、第一次産業である農業・林業と漁業で、乳癌のリスク比がそれぞれ 0.62 (95% CI 0.48-0.78)と 0.21 (95% CI 0.09-0.53)、運動強度の高いの職業で 0.84 (95% CI 0.71-0.97)と低値であった。女性の他の癌種では男性のような傾向は認めなかった。

② 製造業従事者による癌リスクの検討

652 万件中、初回入院で産業登録のあるもののうち、前立腺、乳房、腎、尿管、膀胱、食道、胃、肝臓、膵臓、大腸、肺の癌症例は 155,285 例、更に製造業従事者の症例は 40,370 例であった。

表 5 に製造業における各種癌の分布を示す。乳がんの平均入院時年齢は最も低く 55.1±12.1 歳、他の癌の平均入院時年齢は 65 歳前後であった。腎癌では電気製造業関連業種で 60 歳以下であり、電気機械機器製造業、情報通信機器製造業、電子部品製造業でそれぞれ 59.3 ± 12.9, 55.1 ± 11.7, 56.8 ± 10.7 歳であった。膵癌では石油製品・石炭製品製造業関連となめし革業・同製品・毛皮製造業で 58.0 ± 15.9 、59.8 ± 10.0 歳と 60 歳以下であり、他の業種より低い傾向となった。電子部品・デバイス・電子回路製造業では乳癌、腎癌、胃癌、大腸癌の初回入院時年齢が低い傾向であった（50.7 ± 11.3, 56.8 ± 10.7, 56.6 ± 11.6, 58.6 ± 11.9 歳)。

表 6 は、全 40,370 例を用い、ロジスティック分析で得た各産業のオッズ比を示した。

木材・木製品製造業（家具を除く）では、前立腺、膀胱、食道、胃、肝臓、膵臓、大腸癌のオッズ比が、肝臓癌の 0.51 (95% CI 0.38-0.67) から大腸癌の 0.74 (95% CI 0.61-0.88) と低い傾向が見られた。オッズ比が 2.0 倍以上となったものは、出版・印刷・同関連産業の腎盂尿管癌 2.01(95%CI 1.15-3.52)、ゴム製品製造業の腎盂尿管癌 2.82 (95% CI 1.19-6.70) 、なめし革・同製品・毛皮製造業で 肝臓癌 2.36 (95% CI 1.15-4.83) 、膵臓癌 2.85 (95% CI 1.26-6.47) 、 肺 癌 2.00(95%CI 1.01-3.99)、電気機械器具製造業で腎臓癌 2.49 (95% CI 1.75-3.55), 腎盂尿管癌で 2.09 (1.18-3.70)、情報通信機械器具製造業で腎臓癌 2.69 (95% CI 1.77-4.11)、腎盂尿管癌 2.14

(95% CI 1.02-4.45)、電子部品・デバイス製造業の腎臓癌 2.07(95%CI 1.37-3.13)であった。

なお、オッズ比 2.0 以上と算定された産業と癌の組み合わせに該当する症例、及びなめし革・同製品・毛皮製造業の全癌症例について、その根拠となった症例の病歴サマリから、組織学的所見を確認した。

なめし革・同製品・毛皮製造業の肝臓癌、膵臓癌、肺癌症例、電気機械器具製造業の腎臓癌、尿管癌症例、情報通信機械器具製造業の腎臓癌、尿管癌症例は合計 341 例であった。

これらのうち、2018 年 3 月時点での病歴サマリ取得情報は、閉院やカルテ保存期限を過ぎ入手不可能であったものが 80 例、未到着(破棄等で入手できない可能性も含む)が 111 件であり、残りの 150 件は病歴サマリの取り寄せが終了した。入手したサマリの内容から、病理組織によって癌が特定可能であったものが 139 件、病理組織は同定されないものの、治療によって癌の確定診断と考えられるもの、すなわち近年まで組織採取が困難であった膵癌では化学療法の施行、現在でも組織診断が好ましくないとされる肝臓癌、及び高齢または高度進行にて手術適応とされない腎癌では経皮的肝動脈塞栓療法が施行されたものが 6 例、癌の第一診断病名はあるが、サマリ上で病理組織もしくは治療経過が不明なものが 5 例であった。

D. 考察

① ICOD-Rを用いた癌に対する産業リスクの検討

近年の日本の就業人口は、第一次産業で減少し、第三次産業が急増すると共に、女性の就業人口の増加、高齢化が著しい。また、IT 化により就業内容も変化し、各々の産業が持つハザードやリスクも時代とともに変化している。

以前より、農業・林業は農薬の使用や重量機器の操作など、職業による疾病リスクが高い職種と考えられてきた。一方で、飲酒や喫煙量は少ない傾向が報告されている。同様の傾向は今回の研究の結果と一致した。

第一次産業は定年が無いことが多く、就労人口の高年齢化と直結する。しかし、それを考慮しても癌のリスクが低いということは、これらの職業が癌リスクの低下へ何らかの影響を及ぼしているものと理解して良いだろう。その一つとして産業の運動強度が挙げられる。多くの癌では運動量の低下、続発する肥満と発癌リスクの関連が報告されている。本研究でも、第一次産業を含む運動強度の高い職種で各種癌のリスクは低かった。長年、長時間労働が当たり前であった本邦では、就業中の運動量は生涯の運動量として大きな割合を占めることが、本結果の要因と考えられる。

女性についての解析では、ロジスティック分析で扱った変数量を収束させるのに不十分なサンプル数となった癌種が多く、男性同様の有意差が得られなかった可能性も高い。しかし、十分なサンプル数を得られた乳癌については男性と同様の結果が得られており、職業に基づいた運動量と癌リスクの関係は両性共に存在するものと推測される。

② 各種製造業従事者による癌リスクの検討

本研究では、研究①のように生活習慣病の登録まであるものに絞って症例対照研究とすると多くの症例が失われ、就労人口の少ない職業の統計量が収束しないため、生活習慣病の変数を除外したモデルとした。他方、診断の信頼性を担保するため、高いリスクを呈した群の該当症例に対して、組織学的根拠を可能な限り追跡することとし、該当病歴サマリを直接参照した。該当サマリは労働者健康安全機構を通して全国病院より匿名化した複写が研究者へ提供された。

前立腺、膀胱、食道、胃、肝臓、膵臓、大腸のいずれに於いてもリスクが低い結果となった木材・木製品製造業については、木材粉塵作業によるじん肺、上咽頭癌、鼻腔癌のリスクが報告されているが、発生頻度の高い癌との関連を示唆する報告は見受けられない。有害化学物質の観点から PRTR を参照すると、この業種は他の職種に比べ、届け出対象の化学物質の種類が 31 種類と極めて少ないことが特徴である。この産業の就労人口の年齢特性が癌リスクの低下に寄与しているとは考えにくく、この結果をもたらした要因については更なる検討が必要である。

一方、なめし革・同製品・毛皮製造業では非尿路系である胃、肝臓、膵臓等消化器系と肺癌でリスクが高く、電気機械器具製造業や情報通信機械器具製造業では尿路系である腎臓、腎盂尿管、膀胱癌でリスクが高くなった。なめし革・同製品・毛皮製造業については、途上国で同業務の労働環境の劣悪な状況が高い発癌率と関連するとの報告が多数ある。しかし本邦では、職業選択の余地が幅広く、熟練した職人として好んで当該職業に就く場合が多く、また、労働環境も異なることから、今回の癌リスクの状況は途上国で報告されている結果とは異なる原因と推測される。古くから皮革産業が発達しているイタリアからは今回の報告と同じく同産業の胃癌と膵臓癌と肺癌のリスク増加の報告がなされている。PRTR によると、なめし革・同製品・毛皮製造業では、代謝されてあらゆる臓器へ障害を起こすクロム酸塩の排出量が 22770kg/年と製造業の中でも高い水準である。加えて作業は中小の工房で行われることが多く、作業環境管理が行き届かず、化学物質曝露量が多い可能性も要因として考えられる。

電気機械製造業及び情報通信機械器具製造業に於いて、尿路系癌のリスクが高かった。本邦ではこの業種に特化した報告は未だ見受けられないが、電力及び情報通信業分野の発展は世界中で著しく、同産業の基盤となる半導体製造所での有害作業業務と発癌リスクの報告が中国などから増加している。同産業の作業工程は非常に幅が広いが、アルシンやキノシランなどの揮発性有機化合物をはじめとし、毒性、腐食性の強い化学物質の取り扱いの種類が急増しており、今後新しい作業関連発癌が報告される可能性も高く、本研究結果を鑑みても、注意を要する産業であろう。

E. 結論

本検討では運動強度の高い産業は多くの癌でリスクが低い傾向を認めた。また、有害化学物質暴露の機会が比較的多いと考えられる製造業の中で、癌リスクに特定の傾向のある

ことが示されたが、対象者数の少ないことから生活習慣等の調整を行っていないため、今後さらなる検討が必要である。本研究で示したように、ICOD-R のようなビッグデータの更新作業を継続して行くことにより、癌とリスクを継続的に観察することで、被疑物質曝露による発癌の集積性を洗い出していくことができると考える。

今後、ビックデータから得た結果を補完するため、ミクロデータを用いて重複癌や合併症、予後の解析を継続するとともに、今回使用した ICOD-R と他のビッグデータとの突合などについても検討し、産業ごとの疾患罹患後予後の差と要因について検討していく予定である。

F. 健康危険情報

総括研究報告書に記載

G. 研究発表

1.論文発表

なし

２.学会発表

金子麗奈、豊川智之、小林廉毅. 労働者健康安全機構・病職歴データベースを用いた産業による癌発症リスクの検討. 第 77 回日本公衆衛生学会総会、郡山、2018 年 10 月 26 日

H. 知的財産権の出願・登録状況

なし

表1. Sex and age distribution of all cancers and controls

	ALL		Prostate		Breast		Kidney	
	case	control	case	control	case	control	case	control
Industrial category	57,913	57,913	3,429	3,429	5,093	5,093	1,450	1,450
All	41,957:15,956	41,957:15,956	3,429:0	3,429:0	75:5,018	75:5,018	1,136:314	1,136:314
	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
Agriculture	1,812:1,236	2,569:1,313	149:0	186:0	3:157	2:216	29:20	49:22
	75.9±9.9	75.1±10.8	72.2±9.1	73.4±9.2	69.8±13.5	68.5±14.8	71.9±10.3	71.1±12.1
Fisheries	716:69	957:94	40:0	93:0	0:6	1:24	25:3	33:0
	71.9±9.6	70.0±10.1	68.0±8.7	69.1±9.1	70.3±18.5	63.7±8.1	70.5±11.1	64.5±12.3
Mining	421:14	349:11	29:0	27:0	0:3	2:2	9:0	2:1
	74.1±8.9	73.8±8.5	74.2±8.6	73.2±7.4	58.7±4.2	66.0±9.2	68.4±12.1	71.7±5.7
Construction	6,453:601	6,953:535	439:0	587:0	11:185	11:160	167:10	196:7
	66.5±10.4	65.9±10.4	65.9±8.13	65.1±8.5	56.4±4.2	57.7±12.4	63.2±11.2	62.2±10.2
Manufacturing	11,973:3,059	11,696:2,894	980:0	946:0	21:941	23:878	339:57	315:59
	67.3±10.8	67.4±10.9	66.3±8.6	66.3±8.9	58.2±12.7	58.0±12.7	63.2±12.3	64.8±12.2
Electricity and gas	466:50	491:82	51:0	30:0	0:23	1:33	10:2	6:3
	68.7±10.9	68.1±12.4	68.5±9.4	65.5±10.2	56.6±12.8	57.4±15.0	66.5±11.3	63.8±12.1
Information	481:160	384:175	48:0	24:0	1:69	0:72	33:1	21:4
	61.7±13.5	63.2±14.8	63.0±9.5	65.0±12.7	51.0±13.1	50.9±12.8	55.6±12.9	59.9±15.1
Transport	4,818:363	4,667:315	356:0	364:0	5:126	6:103	109:6	125:6
	67.9±10.6	67.1±10.8	68.2±8.9	65.8±8.2	53.0±12.8	53.9±12.4	64.6±11.0	62.8±12.9
Wholesale and retail	4,744:3,037	4,140:2,864	391:0	341:0	7:1020	8:889	132:60	112:49
	64.8±11.9	65.7±11.9	66.3±8.5	66.7±9.2	55.5±12.9	56.4±12.3	62.1±10.9	62.2±11.1
Finance	818:501	798:523	79:0	77:0	2:198	1:190	28:19	23:10
	64.3±12.7	65.2±12.3	63.1±8.4	65.5±10.2	54.2±12.5	54.1±11.0	59.8±12.9	64.3±12.1
Real estate and rental	466:194	551:165	35:0	43:0	1:76	1:53	16:2	20:5
	65.1±11.9	66.4±11.7	62.8±7.4	65.8±8.8	55.5±11.9	55.4±13.8	65.1±12.3	60.2±12.9
Research and professional services	910:236	774:246	84:0	82:0	2:97	0:97	38:8	16:5
	63.8±11.9	65.1±12.5	63.8±9.7	63.5±7.9	51.4±10.8	53.3±12.8	58.8±12.2	62.6±13.4
Accommodation and dining services	984:1467	946:1,407	63:0	82:0	4:360	1:405	25:33	25:33
	64.5±10.6	65.8±11.7	64.3±7.6	65.0±8.3	58.2±11.8	59.9±12.5	63.9±11.1	62.9±11.8
Amusement services	674:967	777:1004	44:0	68:0	2:282	1:297	12:18	18:21
	65.4±11.8	65.9±11.5	66.1±8.7	65.5±7.6	57.2±13.6	58.2±13.2	65.3±10.9	64.4±13.8
Education	1,279:881	1,255:922	147:0	101:0	4:346	4:312	23:13	29:21
	66.5±12.9	65.5±13.3	64.1±9.4	65.3±10.1	55.7±12.9	52.7±13.0	64.8±13.1	65.2±11.3
Medical and welfare	789:2,126	763:2,266	77:0	65:0	5:789	2:873	21:36	29:42
	60.8±12.8	59.9±12.8	64.7±9.1	64.5±8.8	52.5±11.1	52.6±11.9	58.3±13.5	65.9±13.1
Compound services	512:134	512:152	54:0	39:0	1:55	1:57	11:2	17:3
	67.1±11.2	66.9±12.0	66.9±9.1	66.±8.5	54.5±9.8	57.4±11.5	67.6±7.4	64.9±10.3
Other service industries	1,426:589	1,529:672	107:0	121:0	2:185	6:226	46:17	47:18
	65.2±10.6	65.2±11.3	64.8±8.1	64.5±9.0	59.2±12.4	57.5±11.9	63.0±10.1	63.0±10.7
Government	2,215:272	1,846:316	256:0	153:0	4:100	4:131	63:7	54:5
	68.3±11.2	66.9±12.8	65.1±9.2	66.9±9.86	58.9±13.5	12.5±12.2	64.4±11.3	63.9±13.4
High activity†	14,220:2,283	15,495:2,268	1,013:0	1,257:0	19:477	22:505	339:39	405:36
	69.1±10.9	68.7±11.2	68.0±8.87	66.9±9.0	60.0±14.5	61.7±14.6	65.4±11.4	64.0±11.9
Low activity‡	7,626:2,807	7,265:2,996	762:0	616:0	16:1,057	1:1066	225:68	205:67
	66.1±11.9	65.8±12.4	64.9±9.0	65.5±9.4	55.8±12.6	54.4±12.4	62.8±11.8	63.6±11.9

Distribution of 57,913 cases of common cancers and controls with complete information. Each upper row is age (Mean ± Standard deviation).

The lower row shows the number of cases (male:female) .

†High activity group included agriculture, fisheries, mining and construction; reshown.

‡Low activity group included finance, real estate and rentals, research and professional services, education, compound services, other service industries and government; reshown.

表1. *(continued)*

Industrial category	Ureter case	Ureter control	Bladder case	Bladder control	Esophagus case	Esophagus control	Stomach case	Stomach control
	1,013	1,012	5,964	5,961	2,414	2,414	11,839	11,836
All	828:185	828:185	5314:650	5314:650	2,225:189	2,225:189	9,270:2,569	9,270:2,569
	70.9±9.6	71.0±10.2	70.0±10.7	70.1±11.0	68.6±9.33	68.6±9.7	67.4±11.3	67.4±11.5
Agriculture	36:23	63:19	237:68	346:63	87:18	127:18	475:296	595:259
	78.7±7.9	77.8±9.3	78.0±8.8	77.2±9.2	75.3±8.9	73.7±9.1	75.7±10.3	75.1±10.9
Fisheries	12:1	21:2	84:1	110:6	48:0	57:1	150:17	193:15
	73.4±7.9	72.4±8.6	74.2±10.4	73.2±9.9	70.4±9.5	71.3±9.0	71.3±9.5	70.0±10.1
Mining	5:0	4:0	37:0	38:1	21:0	26:0	81:0	74:3
	69.8±6.6	69.0±14.1	76.2±8.7	73.9±6.9	77.0±6.12	73.7±8.9	74.1±8.3	73.5±8.3
Construction	118:8	127:7	736:26	788:19	359:12	345:6	1,401:104	1,544:94
	69.9±9.3	71.3±8.9	68.3±10.3	67.3±10.9	66.8±8.4	66.9±9.3	65.9±10.5	65.6±10.3
Manufacturing	235:36	251:35	1,595:106	1,519:136	663:44	613:45	2,636:515	2,519:453
	70.9±8.9	70.0±10.2	70.5±9.8	70.1±10.4	69.0±8.9	68.7±8.9	67.7±10.5	67.8±10.7
Electricity and gas	6:0	8:1	47:3	61:1	23:0	24:0	105:6	120:7
	71.8±11.9	69.3±7.5	70.1±10.9	73.1±11.4	67.6±11.6	67.0±11.2	68.2±12.2	68.3±13.4
Information	8:0	12:0	54:2	50:6	19:2	17:2	111:29	90:25
	65.6±11.3	68.1±18.2	63.1±13.9	68.1±12.8	67.9±13.5	68.3±11.0	63.9±13.3	66.6±13.9
Transport	81:2	82:4	633:14	613:20	236:6	246:1	1,058:47	1,040:46
	71.6±8.8	70.9±8.4	70.2±10.2	69.9±10.5	68.5±8.9	67.7±9.3	67.7±10.6	67.1±10.9
Wholesale and retail	77:34	67:32	629:141	541:107	251:24	227:33	1,075:445	920:441
	70.8±10.8	71.1±9.8	69.1±10.7	69.9±11.6	67.9±9.7	68.0±10.1	65.9±11.5	66.7±11.4
Finance	28:8	15:2	114:15	102:27	46:2	58:6	184:62	180:81
	69.8±10.4	71.6±8.1	69.3±12.1	68.9±10.3	69.3±8.5	69.7±9.8	65.8±11.9	67.2±12.2
Real estate and rental	14:3	14:2	42:3	67:7	28:2	25:1	100:29	121:25
	70.1±12.9	67.1±14.4	71.5±13.9	71.3±9.3	70.2±10.6	69.2±10.5	65.8±11.8	67.4±11.8
Research and professional services	22:0	13:4	117:5	92:8	27:2	50:2	187:35	152:37
	69.6±11.5	72.8±9.5	67.2±10.9	67.4±10.6	67.9±10.0	70..4±12.0	65.8±11.9	66.1±12.5
Accommodation and dining services	28:26	11:12	106:55	124:55	81:41	60:15	201:247	216:222
	69.9±8.7	69.9±9.5	67.5±11.4	69.7±12.1	68,.2±10.8	69.0±9.7	65.9±10.7	66.3±11.1
Amusement services	16:14	14:11	84:49	96:52	34:15	51:12	135:152	168:176
	68.3±9.2	67.9±11.3	69.2±10.5	70.9±9.8	65.3±8.7	68.7±9.2	67.2±11.2	66.2±11.5
Education	19:9	29:11	158:35	163:28	71:2	71:7	284:123	291:161
	69.9±9.4	71.7±9.7	72.1±10.9	70.9±11.4	67.6±9.7	68.5±10.3	67.5±12.5	66.7±12.8
Medical and welfare	19:10	17:25	127:87	103:70	31:8	32:29	154:314	170:336
	70.9±9.9	66.2±12.1	68.4±11.6	66.9±13.2	69.5±12.6	63.5±10.3	62.3±13.1	62.7±12.7
Compound services	10:0	15:3	87:1	59:7	21:0	19:0	115:17	117:25
	61.1±8.5	69.2±10.5	70.0±10.2	70.6±11.5	68.0±11.3	68.9±11.8	68.1±11.4	67.4±12.6
Other service industries	37:8	27:13	157:28	179:27	68:7	82:8	320:87	353:118
	69.6±8.3	70.4±10.4	65.6±11.1	68.1±10.9	66.9±9.1	67.9±8.7	65.7±10.7	66.2±10.7
Government	57:3	38:2	270:11	263:10	111:4	95:3	498:44	407:45
	72.5±9.9	72.6±10.5	70.8±10.2	69.7±12.1	68.7±9.5	69.2±11.4	67.8±11.9	67.4±12.7
High activity†	252:34	297:32	1,727:109	1,895:109	751:36	801:26	3,165:464	3,446:417
	72.3±9.4	72.9±9.3	71.0±10.6	70.6±10.9	69.2±9.0	68.9±9.6	69.0±11.1	68.5±11.3
Low activity‡	187:31	151:37	945:98	925:114	372:19	400:27	1,688:397	1,621:492
	70.1±10.2	71.1±10.4	69.5±11.2	69.5±11.2	68.3±9.8	69.0±10.4	66.8±11.8	66.8±12.2

表1. *(continued)*

	Liver		Pancreas		Colon		Lung	
	case	control	case	control	case	control	case	control
Industrial category	2,637	2,637	3,056	3,056	12,470	12,470	8,548	8,548
All	2,032:605	2,032:605	2,181:875	2,181:875	8769:3,701	8769:3,701	6,698:1,850	6,698:1,850
	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
Agriculture	78:57	105:61	91:98	137:116	330:330	510:343	297:169	449:196
	74.1±9.7	74.9±10.2	77.7±10.3	76.5±10.6	76.7±9.9	75.5±10.8	76.4±8.8	75.7±10.1
Fisheries	38:1	56:8	51:5	67:4	146:25	185:25	122:10	141:9
	66.8±8.6	67.5±9.5	71.8±8.7	71.6±9.5	70.9±10.6	69.2±10.4	73.6±7.8	71.2±9.8
Mining	21:1	15:1	18:0	19:1	96:8	63:2	104:2	79:0
	70.0±7.1	74.1±7.6	74.7±9.3	72.1±9.9	74.3±9.4	73.6±9.2	73.8±8.8	75.3±8.8
Construction	354:23	316:22	310:33	384:32	1,377:133	1,490:126	1,181:67	1,165:62
	63.6±9.8	64.5±10.6	68.1±9.6	67.2±9.8	66.1±10.5	65.5±10.9	68.1±9.8	67.3±9.8
Manufacturing	526:108	591:124	597:180	612:168	2,382:715	2,509:671	1,999:357	1,798:325
	67.3±10.6	67.0±10.2	68.6±9.7	68.7±9.9	66.9±11.2	67.2±10.9	68.7±9.9	68.5±10.2
Electricity and gas	30:2	24:4	22:3	32:4	99:6	105:19	73:5	80:10
	69.6±10.8	67.8±11.7	69.8±10.6	68.0±12.4	69.9±10.7	67.5±11.6	70.6±9.4	71.2±10.7
Information	17:4	17:7	35:12	19:9	96:35	90:34	59:6	44:17
	58.4±12.6	64..9±12.9	68.5±10.5	65.7±13.3	63.9±14.0	62.3±14.9	62.9±13.1	64.9±14.5
Transport	269:12	243:8	262:12	230:16	1,029:93	944:73	780:45	774:38
	66.5±11.1	64.9±11.4	68.9±9.9	68.7±9.8	66.9±10.8	66.7±10.8	69.0±9.8	68.3±10.1
Wholesale and retail	217:112	216:107	253:161	197:181	1,038:697	838:700	674:343	673:325
	66.6±10.7	66.5±12.0	68.7±10.3	67.9±10.9	65.1±11.5	66.0±11.8	66.6±10.2	67.7±10.3
Finance	27:23	42:13	34:26	36:24	172:100	149:119	104:48	115:51
	67.8±10.9	67.0±12.3	66.3±9.4	66.2±10.2	65.3±12.2	65.1±11.9	66.9±11.9	68.9±11.3
Real estate and rental	24:8	30:3	26:8	27:4	115:45	132:45	65:18	71:20
	66.9±13.2	69.4±10.9	64.5±10.7	69.7±8.3	66.6±10.7	66.5±10.6	67.5±10.6	66.6±11.5
Research and professional services	49:5	29:2	50:13	36:13	221:53	185:40	113:18	119:38
	64.7±11.3	65.9±12.4	67.9±11.3	67.7±12.4	63.5±11.4	64.7±11.7	65.0±10.7	67.6±12.4
Accommodation and dining services	55:83	38:70	41:68	47:75	218:354	200:342	162:200	142:178
	64.7±10.3	68.5±9.2	65.6±9.9	70±10.7	65.4±9.9	65.5±11.9	65.7±9.8	68.1±10.3
Amusement services	38:37	31:33	45:61	45:55	157:207	168:218	107:132	117:129
	68.1±10.8	67.2±11.3	67.3±9.9	68.7±8.3	65.4±11.2	67.1±10.6	66.5±10.0	67.9±9.1
Education	58:34	59:37	83:50	65:35	288:194	239:223	144:75	204:87
	70.2±11.4	66.2±10.9	70.2±10.6	69.7±12.1	67.4±12.9	67.1±12.5	69.2±11.4	68.5±11.9
Medical and welfare	33:66	41:72	40:103	40:92	179:469	150:488	103:244	114:239
	67.5±10.1	63.4±10.2	66.4±11.4	66.1±10.1	62.1±11.5	61.3±11.6	64.3±10.9	63.9±11.0
Compound services	21:4	25:4	23:6	29:10	88:34	107:25	81:15	84:18
	65.9±13.1	70.4±15.6	70.4±14.3	69.1±10.2	67.3±10.7	66.6±10.6	68.9±10.9	67.3±12.5
Other service industries	66:23	78:20	83:27	75:21	300:130	314:131	240:77	248:90
	65.9±10.5	65.3±10.8	65.7±9.2	66.4±8.6	65.7±10.8	64.9±11.7	66.8±9.7	66.8±11.0
Government	111:2	76:10	117:9	84:15	438:73	391:77	290:19	281:18
	67.8±11.7	67.6±12.3	69.7±10.3	68.3±13.4	69.1±11.6	66.8±12.9	70.5±10.2	69.4±11.3
High activity[†]	760:94	735:100	732:148	837:169	2,978:589	3,192:569	2,484:293	2,608:305
	66.8±11.1	67.1±11.4	70.8±10.5	70.3±10.7	68.8±11.3	68.4±11.5	70.3±10.0	69.8±10.5
Low activity[‡]	356:99	339:89	416:139	352:122	1,622:629	1.157:660	1,037:270	1,122:322
	67.2±11.7	66.9±11.8	68.2±10.6	68.1±11.2	66.7±11.8	66.0±12.1	68.1±10.8	68.1±11.6

表2. Distribution of life-related diseases for each industrial group

Industrial category	Brinkman Index†		Alcohol(g/day)†		Hypertension‡		Hyperlypidemia‡	
	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)	6,726(11.6)	6,866(11.8)
Agriculture	0(0:760)	0(0:630)	0(0:56.0)	0(0:400)	1,172(38.5)	1,403(36.1)	237(7.8)	257(6.6)
Fisheries	735(200:1060)	600(0:1000)	52.8(0:95.0)	460(0:900)	320(40.8)	336(32.0)	60(7.6)	53(5.0)
Mining	611(300:960)	550(82:900)	47.0(0:85.5)	78(0:825)	186(42.8)	137(38.1)	47(10.8)	30(8.3)
Construction	660(240:980)	530(38:880)	52.0(0:90.0)	356(0:800)	2,554(36.2)	2,493(33.3)	679(9.6)	679(9.1)
Manufacturing	470(0:840)	300(0:740)	30.0(0:76.0)	90(0:600)	5,267(35.0)	5,321(36.5)	1,678(11.2)	1,757(12.1)
Electricity and gas	540(40:860)	180(0:580)	50.0(0:80.0)	0(0:400)	204(39.5)	203(35.4)	79(15.3)	69(12.0)
Information	340(0:700)	180(0:720)	20.0(0:60.0)	0(0:400)	200(31.2)	176(31.5)	124(19.3)	142(25.4)
Transport	600(250:980)	510(70:900)	50.0(0:90.0)	390(0:800)	1,915(40.0)	1,749(35.1)	513(9.9)	568(11.4)
Wholesale and retail	300(0:780)	137(0:620)	4.8(0:66.0)	0(0:500)	2,552(32.8)	2,258(32.2)	873(11.2)	772(11.0)
Finance	300(0:760)	175(0:720)	5.0(0:66.0)	5.0(0:600)	438(33.2)	391(29.6)	230(17.4)	184(13.9)
Real estate and rental	400(0:840)	327(0:780)	21.8(0:71.2)	110(0:670)	216(32.7)	207(28.9)	74(11.2)	46(6.4)
Research and professional services	440(0:820)	295(0:700)	28.5(0:74.0)	60(0:560)	375(32.7)	326(32.0)	161(14.1)	187(18.3)
Accommodation and dining services	255(0:740)	49(0:540)	0(0:60.0)	0(0:400)	801(32.7)	745(31.7)	205(8.4)	282(12.0)
Amusement services	30(0:590)	0(0:500)	0(0:41.0)	0(0:280)	529(32.2)	571(32.2)	166(10.1)	194(10.9)
Education	0(0:560)	0(0:400)	0(0:40.0)	0(0:204)	730(33.8)	690(31.7)	356(16.5)	340(15.6)
Medical and welfare	0(0:320)	0(0:230)	0(0:21.6)	0(0:140)	785(26.9)	878(29.0)	528(18.1)	610(20.2)
Compound services	400(0:800)	216(0:690)	25.5(0:72.0)	0(0:600)	225(34.8)	221(33.3)	81(12.5)	115(17.3)
Other service industries	430(0:860)	200(0:675)	21.6(0:75.0)	30(0:600)	660(32.8)	686(31.2)	239(11.9)	185(8.4)
Government	525(25:880)	300(0:740)	40.0(0:80.0)	120(0:600)	970(39.0)	670(31.0)	396(15.9)	396(18.3)
High activity §	600(42:960)	450(0:860)	42.0(0:86.0)	240(0:760)	6,147(37.3)	6,118(34.4)	1,536(9.3)	1,587(8.9)
Low activity ¶	370(0:800)	192(0:650)	20.0(0:70.0)	0(0:552)	3,614(34.6)	3,191(31.1)	1,537(14.7)	1,453(14.2)

†The amount of Brinkman Index and alcohol consumption. Median (IQR25%:75%) IQR:Interquartile range.

‡The number of historical life-related diseases (%).

§ High activity group included agriculture, fisheries, mining and construction; reshown. ¶Low activity group included finance, real estate and rentals, research and professional services, education, compound services, other service industries and government; reshown.

表 2. *(continued)*

Industrial category	Hyperuricemia‡		Diabetes‡		Obesity‡	
	case	control	case	control	case	control
All	1,769(3.1)	1,778(3.1)	8,683(15.0)	9,206(15.9)	7,451(12.9)	6,912(11.9)
Agriculture	47(1.5)	41(1.1)	399(13.1)	639(16.5)	200(6.6)	229(5.9)
Fisheries	22(2.8)	14(1.3)	144(18.3)	146(13.9)	61(7.8)	46(4.4)
Mining	11(2.5)	7(1.9)	65(14.9)	87(24.2)	21(4.8)	25(6.9)
Construction	224(3.2)	204(2.7)	1,193(16.9)	1,104(14.7)	817(11.6)	855(11.4)
Manufacturing	473(3.2)	509(3.5)	2,197(14.6)	2,459(16.9)	1,992(13.3)	1,770(12.1)
Electricity and gas	27(5.2)	40(6.9)	90(17.4)	107(18.7)	75(14.5)	88(15.4)
Information	42(6.6)	41(7.3)	95(14.8)	60(10.7)	110(17.2)	107(19.1)
Transport	159(3.1)	225(4.5)	886(17.1)	1,042(20.9)	684(13.2)	660(13.3)
Wholesale and retail	224(2.9)	169(2.4)	1,116(14.3)	1,055(15.1)	970(12.5)	858(12.3)
Finance	58(4.4)	89(6.7)	191(14.5)	161(12.2)	225(17.1)	179(13.6)
Real estate and rental	23(3.5)	6(0.8)	113(17.1)	140(19.5)	85(12.9)	100(13.9)
Research and professional services	64(5.6)	43(4.2)	164(14.3)	99(9.7)	178(15.5)	135(13.2)
Accommodation and dining services	41(1.7)	37(1.6)	312(12.7)	472(20.1)	283(11.6)	308(13.1)
Amusement services	31(1.9)	54(3.0)	228(11.9)	245(13.8)	203(12.4)	162(9.1)
Education	62(2.9)	102(4.7)	325(15.1)	285(13.1)	350(16.2)	282(13.0)
Medical and welfare	77(2.6)	51(1.7)	285(9.8)	299(9,9)	406(13.9)	389(12.9)
Compound services	16(2.5)	28(4.2)	121(18.7)	104(15.7)	111(17.2)	122(18.4)
Other service industries	43(2.1)	56(2.5)	324(16.1)	319(14.5)	246(12.2)	241(11.0)
Government	125(5.0)	62(2.9)	435(17.5)	383(17.7)	434(17.5)	356(16.5)
High activity §	463(2.8)	491(2.8)	2,687(16.3)	3,018(16.9)	1,783(10.8)	1,815(10.2)
Low activity ¶	391(3.8)	386(3.8)	1,673(16.0)	1,491(14.5)	1,629(15.6)	1,415(13.8)

表 3. Odds ratio of each industry to cancer in males

Industrial category	Prostate	Kidney	Ureter	Bladder	Esophagus	Stomach	Liver	Pancreas	Colon	Lung
Numbers of cases	3,429	1,136	828	5,314	2,225	9,270	2,032	2,181	8,769	6,698
Agriculture	0.66(0.50−0.87)	0.53(0.31−0.92)	0.47(0.27−0.86)	0.57(0.46−0.71)	0.58(0.41−0.85)	0.68(0.58−0.80)	0.71(0.49−0.96)	0.51(0.36−0.72)	0.50(0.42−0.59)	0.69(0.57−0.85)
	0.004**	0.023*	0.013*	0.000**	0.004**	0.000**	0.041*	0.000**	0.000**	0.000**
Fisheries	0.37(0.24−0.56)	0.61(0.33−1.15)	0.45(0.20−1.01)	0.61(0.45−0.85)	0.68(0.43−1.10)	0.58(0.45−0.73)	0.63(0.38−0.98)	0.57(0.37−0.89)	0.59(0.46−0.76)	0.69(0.52−0.94)
	0.000**	0.126	0.055	0.003**	0.113	0.000**	0.055	0.015*	0.000**	0.017*
Mining	0.89(0.49−1.63)	3.30(0.68−16.16)	1.31(0.32−5.45)	0.80(0.49−1.31)	0.64(0.32−1.25)	0.95(0.67−1.34)	1.58(0.73−3.42)	0.65(0.37−1.53)	1.14(0.81−1.59)	1.25(0.87−1.81)
	0.726	0.139	0.704	0.381	0.192	0.792	0.242	0.442	0.444	0.211
Construction	0.65(0.54−0.79)	0.73(0.51−1.02)	0.78(0.51−1.21)	0.78(0.66−0.91)	0.83(0.65−1.07)	0.75(0.66−0.84)	1.02(0.79−1.32)	0.62(0.48−0.79)	0.73(0.64−0.82)	0.96(0.82−1.11)
	0.000**	0.069	0.278	0.002**	0.154	0.000**	0.827	0.000**	0.000**	0.555
Manufacturing	0.88(0.74−1.05)	0.93(0.69−1.27)	0.85(0.57−1.26)	0.92(0.80−1.06)	0.98(0.78−1.24)	0.92(0.83−1.01)	0.89(0.69−1.12)	0.79(0.63−0.98)	0.76(0.68−0.86)	1.19(1..04−1.37)
	0.163	0.661	0.415	0.246	0.892	0.103	0.314	0.039*	0.000**	0.012*
Electricity and gas	1.44(0.90−2.32)	1.33(0.47−3.85)	0.63(0.20−2.01)	0.72(0.47−1.08)	0.80(0.41−1.58)	0.79(0.59−1.04)	1.36(0.75−2.47)	0.49(0.26−0.90)	0.76(0.57−1.02)	1.19(0.82−1.74)
	0.132	0.587	0.429	0.116	0.531	0.099	0.310	0.022*	0.074	0.363
Information	1.73(1.03−2.90	1.36(0.73−2.55)	0.66(0.24−1.78)	0.95(0.63−1.43)	1.08(0.53−2.20)	1.03(0.77−1.40)	1.10(0.53−2.30)	1.44(0.79−2.61)	0.86(0.64−1.17)	1.52(0.98−2.36)
	0.037*	0.324	0.411	0.814	0.829	0.800	0.801	0.232	0.351	0.065
Transport	0.84(0.68−1.04)	0.71(0.49−1.03)	0.89(0.55−1.42)	0.86(0.73−1.01)	0.83(0.63−1.09)	0.85(0.74−0.96)	1.01(0.77−1.33)	0.86(0.66−1.12)	0.86(0.76−0.98)	0.99(0.84−1.16)
	0.102	0.072	0.617	0.076	0.177	0.747	0.928	0.268	0.028*	0.856
Wholesale and retail (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)
	−	−	−	−	−	−	−	−	−	−
Finance	0.86(0.61−1.22)	1.13(0.46−3.85)	1.48(0.71−3.09)	0.95(0.60−1.27)	0.71(0.45−1.12)	0.88(0.69−1.10)	0.64(0.38−1.10)	0.78(0.46−1.32)	0.93(0.73−1.18)	0.81(0.59−1.11)
	0.414	0.693	0.298	0.724	0.149	0.696	0.109	0.365	0.542	0.192
Real estate and rental	0.73(0.45−1.17)	0.81(0.38−1.69)	1.00(0.43−2.34)	0.49(0.32−0.74)	0.94(0.53−1.71)	0.76(0.57−1.01)	0.78(0.43−1.42)	0.73(0.41−1.30)	0.71(0.54−0.93)	0.99(0.68−1.47)
	0.452	0.572	0.996	0.001**	0.850	0.568	0.421	0.286	0.013*	0.998
Research and professional services	0.86(0.61−1.21)	2.21(1.13−4.36)	1.57(0.69−3.54)	1.10(0.81−1.49)	0.45(0.27−0.76)	1.06(0.84−1.34)	1.76(1.05−2.97)	1.09(0.67−1.76)	0.96(0.78−1.12)	0.99(0.73−1.36)
	0.605	0.021**	0.281	0.530	0.003**	0.639	0.033*	0.713	0.768	0.990
Accommodation and dining services	0.70(0.49−1.17)	0.84(0.44−1.56)	2.03(1.01−4.53)	0.77(0.58−1.02)	1.21(0.81−1.82)	0.78(0.63−0.97)	1.42(0.90−2.27)	0.69(0.44−1.12)	0.89(0.72−1.10)	1.18(0.89−1.56)
	0.482	0.576	0.085	0.075	0.34	0.028*	0.138	0.137	0.286	0.258
Amusement services	0.55(0.36−0.85)	0.64(0.29−1.41)	1.10(0.48−2.51)	0.76(0.55−1.05)	0.58(0.35−0.97)	0.73(0.57−0.94)	1.21(0.71−2.09)	0.79(0.50−1.24)	0.77(0.61−0.98)	0.81(0.59−1.16)
	0.006**	0.266	0.830	0.104	0.039*	0.014∗	0.485	0.316	0.038*	0.198
Education	1.15(0.86−1.55)	0.68(0.37−1.25)	0.62(0.31−1.21)	0.88(0.68−1.13)	0.88(0.59−1.31)	0.92(0.76−1.12)	0.97(0.64−1.49)	1.06(0.62−1.57)	0.98(0.80−1.20)	0.91(0.69−1.19)
	0.349	0.221	0.159	0.313	0.516	0.413	0.907	0.751	0.844	0.508
Medical and welfare	0.94(0.65−1.37)	0.66(0.35−1.24)	1.03(0.48−2.21)	1.08(0.81−1.45)	0.63(0.47−1.47)	0.79(0.63−1.02)	0.89(0.53−1.51)	0.84(0.52−1.37)	0.98(0.80−1.20)	1.13(0.18−1.57)
	0.745	0.202	0.942	0.593	0.526	0.068	0.673	0.496	0.929	0.452
Compound services	1.87(0.76−1.86)	0.61(0.26−1.42)	0.55(0.22−1.35)	1.34(0.94−1.92)	1.12(0.56−2.27)	0.86(0.65−1.13)	0.98(0.52−1.85)	0.69(0.39−1.26)	0.65(0.48−0.87)	1.22(0.85−1.74)
	0.454	0.248	0.195	0.106	0.743	0.292	0.953	0.237	0.005*	0.282
Other service industries	0.77(0.57−1.04)	0.87(0.53−1.42)	1.22(0.66−2.25)	0.75(0.58−0.96)	0.68(0.46−1.02)	0.77(0.65−0.92)	0.83(0.56−1.23)	0.84(0.58−1.21)	0.76(0.66−0.92)	0.99(0.79−1.25)
	0.095	0.575	0.517	0.023*	0.063	0.004**	0.359	0.343	0.004*	0.953
Government	1.40(0.85−1.79)	0.98(0.62−1.54)	1.31(0.75−2.28)	0.88(0.71−1.08)	1.04(0.64−1.47)	1.04(0.88−1.22)	1.52(1.05−2.19)	1.09(0.77−1.53)	0.90(0.77−1.07)	1.05(0.84−1.30)
	0.009**	0.938	0.350	0.235	0.824	0.638	1.059	0.626	0.255	0.686
High activity†	0.70(0.59−0.83)	0.69(0.51−0.95)	0.44(0.26−0.74)	0.77(0.67−0.88)	0.78(0.62−0.97)	0.76(0.69−0.85)	0.67(0.48−0.93)	0.67(0.54−0.84)	0.74(0.66−0.82)	0.69(0.57−0.84)
	0.000**	0.020*	0.002**	0.000**	0.028*	0.000**	0.048*	0.000**	0.000**	0.000**
Low activity ‡	1.05(0.88−1.27)	0.96(0.70−1.33)	1.06(0.71−1.60)	0.88(0.76−1.03)	0.82(0.64−1.04)	0.91(0.82−1.02)	1.06(0.83−1.37)	0.94(0.74−1.20)	0.86(0.76−0.97)	0.99(0.85−1.15)
	0.534	0.827	0.760	0.106	0.101	0.123	0.607	0.616	0.012*	0.960

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 wholesale and retail as a reference (ref).

The lower row shows a p−value of <0.01** or <0.05* were considered to be statistically significant

†High activity group included agriculture, fisheries, mining and construction; reshown.

‡Low activity group included finance, real estate and rentals, research and professional services, education, compound services, other service industries and government; reshown.

表4. Odds ratio of each industry to cancers in females

Industrial category	Breast	Kidney	Ureter	Bladder	Esophagus	Stomach	Liver	Pancreas	Colon	Lung
Number of cases	5,018	314	185	650	189	2,569	605	875	3,701	1,850
Agriculture	0.62(0.48–0.78)	0.72(0.31–1.59)	0.97(0.40–.32))	0.92(0.55–1.53)	2.43(0.85–6.99)	1.19(0.94–1.51)	0.91(0.56–1.47)	0.90(0.61–1.35)	0,98(0.80–1.21)	0.85(0.63–1.14)
	0.000**	0.409	0.941	0.744	0.099	0.146	0.699	0.620	0.868	0.273
Fisheries	0.21(0.09–0.53)	NA	NA	0.11(0.01–0.94)	NA	1.15(0.54–2.45)	0.13(.02–1.09)	1.38(0.30–6.42)	1.00(0.56–1.81)	0.93(0.35–2.51)
	0.001**	NA	NA	0.044*	NA	0.710	0.061	0.683	0.987	0.893
Mining	1.34(0.22–8.17)	NA	NA	NA	NA	NA	0.85(0.05–14.82)	NA	4.34(0.92–20.6)	NA
	0.75	NA	NA	NA	NA	NA	0.911	NA	0.064	NA
Construction	0.99(0.78–1.24)	1.21(0.42–3.48)	0.79(0.24–2.62)	1.10(0.55–2.21)	3.65(0.85–15.62)	1.08(0.79–1.49)	0.95(.45–1.83)	1.18(0.69–2.05)	1.05(0.81–1.34)	0.97(0.65–1.46)
	0.901	0.715	0.699	0.773	0.081	0.618	0.880	0.540	0.718	0.892
Manufacturing	0.95(0.83–1.07)	0.76(0.43–1.35)	0.83(0.39–1.77)	0.65(0.45–0.94)	1.62(0.74–3.56)	1.13(0.94–1.37)	0.84(0.57–1.25)	1.25(0.90–1.73)	1.07(0.93–1.25)	1.03(0.82–1.29)
	0.406	0.350	0.623	0.023*	0.228	0.187	0.388	0.178	0.339	0.793
Electricity and gas	0.64(0.37–1.10)	0.39(0.05–3.05)	NA	1.69(0.16–18.30)	NA	0.78(0.26–2.38)	0.46(0.08–2.71)	0.85(0.18–4.00)	0.32(0.12–0.79)	0.53(0.18–1.61)
	0.109	0.376	NA	0.666	NA	0.669	0.38	0.838	0.015*	0.63
Information	0.82(0.58–1.16)	0.13(0.02–1.44)	NA	0.24(0.47–1.31)	5.42(0.50–58.6)	1.11(0.64–1.93)	0.56(0.16–2.02)	1.2(0.62–3.75)	1.07(0.65–1.76)	0.37(0.14–0.96)
	0.262	0.096	NA	0.100	0.164	0.721	0.377	0.364	0.782	0.042*
Transport	1.12(0.84–1.49)	0.72(0.21–2.45)	0.35(0.05–2.49)	0.54(0.25–1.15)	–	0.96(0.61–1.49)	1.28(0.45–3.37)	0.70(0.32–1.57)	1.28(0.92–1.78)	1.18(0.73–1.94)
	0.843	0.602	0.299	0.108	0.990	0.849	0.620	0.387	0.137	0.491
Wholesale and retail (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)
	–	–	–	–	–	–	–	–	–	–
Finance	0.90(0.72–1.12)	1.69(0.68–4.24)	4.42(0.82–23.92)	0.49(0.24–0.98)	0.32(0.04–2.57)	0.3(0.51–1.05)	1.50(0.9–3.23)	1.21(0.65–2.22)	0.84(0.63–1.12)	0.86(0.55–1.3)
	0.721	0.255	0.085	0.045*	0.282	0.092	0.297	0.549	0.234	0.493
Real estate and rental	1.22(0.85–1.75)	0.26(0.41–1.72)	1.29(0.20–8.18)	0.31(0.07–1.34)	2.14(0.15–30.44)	1.11(0.63–1.96)	1.82(0.45–7.34)	1.99(0.57–6.92)	1.03(0.67–1.58)	0.72(0.36–1.45)
	0.849	0.162	0.790	0.118	0.572	0.712	0.399	0.281	0.881	0.361
Research and professional services	0.89(0.66–1.20)	1.45(0.41–5.17)	NA	0.49(0.15–1.66)	1.25(0.16–0.58)	0.89(0.54–1.48)	2.64(0.50–13.96)	1.17(0.50–2.76)	1.1(0.86–2.01)	0.48(0.26–0.87)
	0.66	0.564	NA	0.255	0.828	0.675	0.252	0.16	0.206	0.016*
Accommodation and dining services	0.80(0.68–0.95)	0.76(0.40–1.44)	1.85(0.73–4.69)	0.72(0.46–1.14)	3.81(1.51–9.64)	1.04(0.63–1.31)	0.98(0.63–1.52)	0.91(0.60–1.34)	1.01(0.84–1.22)	0.82(0.62–1.08)
	0.677	0.400	0.192	0.162	0.005	0.699	0.930	0.643	0.881	0.154
Amusement services	0.84(0.69–1.01)	0.68(0.32–1.43)	0.83(0.8–2.47)	0.79(0.49–1.28)	1.36(0.45–4.15)	0.3(0.64–1.07)	1.15(0.64–2.05)	1.24(0.79–1.93)	0.95(0.76–1.19)	0.89(0.65–1.21)
	0.692	0.307	0.741	0.336	0.585	0.152	0.645	0.340	0.657	0.447
Education	0.95(0.80–1.14)	0.50(0.22–1.17)	0.56(0.17–1.81)	1.02(0.57–1.83)	0.49(0.06–3.62)	0.75(0.57–0.99)	1.04(0.60–1.80)	1.68(1.03–2.75)	0.89(0.71–1.09)	0.84(0.58–1.20)
	0.795	0.110	0.332	0.942	0.481	0.046*	0.878	0.036*	0.259	0.337
Medical and welfare	0.78(0.68–0.89)	0.76(0.42–1.38)	0.29(0.11–0.79)	1.01(0.65–1.56)	0.31(0.09–0.99)	0.92(0.75–1.13)	0.93(0.59–1.45)	1.22(0.85–1.74)	0.97(0.82–1.14)	0.94(0.73–1.20)
	0.68	0.372	0.016	0.958	0.050	0.449	0.752	0.283	0.705	0.611
Compound services	0.80(0.54–1.17)	0.43(0.65–2.82)	NA	0.10(0.01–0.89)	NA	0.6(0.35–1.23)	0.78(0.17–3.47)	0.57(0.18–1.82)	1.37(0.81–2.34)	0.87(0.43–1.77)
	0.539	0.380	NA	0.039*	NA	0.188	0.742	0.349	0.237	0.707
Other service industries	0.71(0.57–0.88)	0.63(0.28–1.45)	0.42(0.14–1.27)	0.89(0.49–1.61)	2.74(0.68–11.02)	0.71(0.52–0.98)	1.02(0.50–2.09)	1.39(0.74–2.61)	0.98(0.75–1.27)	0.77(0.54–1.11)
	0.573	0.283	0.125	0.695	0.154	0.037*	0.954	0.299	0.757	0.157
Government	0.64(0.49–0.84)	1.68(0.45–6.31)	1.55(0.23–10.33)	1.17(0.47–2.89)	2.98(0.34–26.3)	0.98(0.63–1.54)	0.21(0.04–1.03)	0.62(0.26–1.49)	0.96(0.681.35)	1.17(0.58–2.38)
	0.485	0.439	0.648	0.736	0.325	0.945	0.055	0.287	0.810	0.660
High activity†	0.84(0.71–0.97)	0.89(0.48–1.66)	0.88(0.43–1.78)	0.83(0.56–1.24)	2.31(0.96–5.56)	1.19(0.95–1.50)	0.86(0.58–1.29)	0.94(0.67–1.31)	1.06(0..91–1.26)	0.94(0.74–1.21)
	0.000**	0.701	0.721	0.406	0.063	0.248	0.473	0.644	0.440	0.291
Low activity‡	0.85(0.75–1.96)	0.85(0.49–1.47)	1.05(0.82–1.55)	0.70(0.47–1.03)	1.23(0.53–2.86)	0.78(0.62–0.95)	1.07(0.72–1.60)	1.26(0.89–1.77)	0.95(0.83–1.12)	0.81(0.64–1.02)
	0.572	0.582	0.346	0.068	0.630	0.012	0.738	0.181	0.591	0.072

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 wholesale and retail as a reference(ref).

The lower row shows p–values of <0.01** or <0.05* were considered to be statistically significant

NA: Data was not available for a number of cases, which were thus too small.

†High activity group included agriculture, fisheries, mining and construction; reshown.

‡Low activity group included finance, real estate and rentals, research and professional services, education, compound services, other service industries and government; reshown.

表5. Sex and age distribution of all cancers and manufacturing industrial categories

		ALL	Prostate	Breast	Kidney	Ureter	Bladder
Industrial category		40,370	2,769	2,462	1,149	454	3,639
All		32,238:8,132	2769:0	49:2,413	978:171	430:64	3,376:263
	40,370	65.3±11.4	68.8±9.0	55.5±12.1	62.5±11.5	69.4±9.9	68,.5±11.2
Food		1,856:1,714	165:0	7:464	44:33	26:7	196:61
	3570	63.6±11.5	69.6±8.56	56.3±11.1	61.1±11.9	68.9±10.5	68.2±11.7
Beverages, tobacco and feed		474:138	52:0	3:40	11:4	7:3	50:3
	612	65.9±10.8	70.8±9.4	55.7±12.5	63.8±12.8	69.3±6.4	67.6±11.6
Textile mill products		729:293	62:0	1:74	27:5	15:2	80:11
	1022	68.0±11.4	71.6±7.91	59.9±12.1	65.1±8.5	70.3±7.9	72.6±11.3
Clothes and other textiles		595:1,126	50:0	0:340	20:19	6:15	67:28
	1721	64.1±11.8	68.5±11.2	57.3±11.5	65.4±11.7	72.3±10.2	67.5±12.9
Lumber and wood products, except furniture		1,129:190	94:0	2:49	35:5	16:4	112:8
	1319	67.1±11.5	70.4±10.3	56.2±12.6	65.7±13.5	71.8±8.12	69.8±11.6
Furniture and fixtures		561:91	63:0	1:25	17:6	11:1	57:4
	652	66.2±11.1	70.7±9.7	57.7±11.4	60.4±8.3	74.5±7.82	68.8±9.5
Pulp, paper and paper products		871:194	90:0	2:54	28:4	6:1	84:8
	1065	75.8±11.2	67.0±9.8	58.1±12.4	62.5±11.1	68.1±10.2	66.9±10.5
Printing and allied industries		1,067:249	84:0	0:94	35:6	23:0	130:5
	1316	65.2±11.8	67.8±9.2	54.5±13.4	60.5±11.1	72.0±9.2	67.3±12.0
Chemicals, and chemical and allied products		3,299:357	350:0	0:143	102:11	38:0	336:11
	3656	66.5±11.4	69.9±9.4	52.4±12.2	63.1±11.3	70.6±9.1	68.4±11.2
Petroleum and coal products		339:21	33:0	0:7	12:0	3;0	36:2
	360	63.7±11.4	67.7±8.51	45.6±13.2	62.4±9,6	75.6±9.3	65.9±11.2
Plastic produsts, except otherwise classified		421:178	28:0	1:62	16:4	4:1	34:7
	599	62.4±11.1	63.8±7.8	58.2±10.7	56.8±8.8	67.8±8.5	65.9±12.3
Rubber products		248:68	18:0	0:22	8:3	6:1	35:0
	316	64.7±11.8	71.3±9.3	54.3±12.9	64.2±12.4	60.4±11.3	69.5±10.3
Leather tannning, leather products and fur		75:31	5:0	0:10	2:1	1:0	8:0
	106	61.3±11.1	69.6±9.1	48.8±11.4	70.6±4.2	−	64.3±14.7
Ceramic, stone and clay products		1,878:289	139:0	4:72	45:4	28:1	196:14
	2167	66.5±10.9	69.8±8.7	58.2±13.5	63.5±11.5	65.9±11.1	70.0±10.4
Iron and steel		3,746:224	348:0	6:70	106:2	48:0	393:7
	3970	66.1±10.6	69.1±8.7	54.0±11.1	64.5±10.4	68.1±9.0	68.9±10.1
Non−ferrous metals and products		990:101	84:0	3:38	29:2	13:0	112:4
	1091	66.3±10.9	68.9±8.25	55.6±11.7	64.8±11.1	60.3±10.1	68.1±11.0
Fabricated metal products		3,823:791	279:0	3:192	93:13	36:8	342:29
	4614	66.1±10.6	67.5±8.4	58.0±11.9	63.9±10.6	72.3±10.5	69.1±9.9
General purpose machinery		3,546:446	306:0	6:149	122:8	51:2	377:14
	3992	65.5±11.4	69.3±7.8	55.1±13.3	64.2±11.9	68.6±10.9	68.3±10.8
Electrical machinery, equipment and supplies		1,153:344	98:0	2:100	51:12	19:2	125:10
	1497	62.7±12.2	64.1±8.4	49.4±12.1	59.3±12.9	63.5±11.1	68.7±12.4
Information and communication electronics		585:198	58:0	1:77	28:7	9:1	65:4
	783	61.4±12.7	66.6±9.53	51.1±9.7	55.1±11.7	67.9±8.9	61.7±15.3
Electronic parts, devices and electronic circuits		521:316	37:0	0:104	27:9	9:2	60:6
	837	58.8±11.9	62.6±8.9	50.7±11.3	56.8±10.7	68.9±6.3	64.1±11.5
Transportation equipment		3,306:362	251:0	5:103	91:5	45:8	368:14
	3666	66.2±11.2	68.9±8.7	54.1±11.8	62.8±10.8	69.5±10.1	69.5±10.8
Precision machinery		386:101	29:0	2:41	12:0	1:0	41:2
	487	62.2±11.5	65.5±8.8	54.3±12.5	55.2±9.56	−	65.6±10.0
Miscellaneous manufacturing industries		659:293	46:0	0:83	17:8	9:5	72:11
	952	66.0±11.7	71.7±10.7	56.5±13.1	61.1±14.6	72.3±6.3	68.6±11.4

Distribution of 40,370 cases of common cancers with complete information. Each upper row is age (mean±standard deviation).
Each lower row shows the number of cases (male:female) .

表5.（*continued.*）

		Esophagus	Stomach	Liver	Pancreas	Colon	Lung
Industrial category		1,730	9,741	2,869	1,944	7,758	5,815
All		1,612:118	7,989:1,752	2,518:351	1,535:409	5,991:1,767	4,991:824
	40,370	66.4±9.6	64.1±11.7	64.2±10.5	66.4±10.6	65.6±11.1	67.5±10.5
Food		121:28	457:375	164:81	98:98	317:378	262:188
	3570	65.3±8.9	62.7±11.4	63.5±10.6	65.3±9.9	64.9±11.1	64.9±11.2
Beverages, tobacco and feed		35:0	110:27	39:8	33:3	81:34	53:16
	612	68.1±6.4	63.8±11.2	66.7±8.2	67.3±9.8	65.9±10.0	68.6±9.8
Textile mill products		40:7	175:65	71:16	38:19	106:69	114:25
	1022	68.3±9.5	67.6±11.6	63.9±11.1	69.1±12.3	68.3±11.3	70.2±10.6
Clothes and other textiles		27:13	160:228	50:55	37:50	116:247	64:129
	1721	67±11.4	64.2±11.6	65.4±9.8	65.5±11.9	66.2±10.9	65.9±10.5
Lumber and wood products, except furniture		57:2	299:39	74:8	55:10	186:46	199:19
	1319	66.4±10.9	65.7±11.1	65.6±9.1	69.6±9.5	67.1±11.8	68.9±11.3
Furniture and fixtures		26:0	131:23	39:2	19:3	111:23	86:4
	652	66.7±8.5	64.7±12.5	64.4±12.5	67.2±10.7	65.6±10.5	68.4±10.0
Pulp, paper and paper products		51:2	217:44	58:14	39:12	169:37	127:18
	1065	67.5±10.1	63.6±11.8	62.3±11.2	64.6±10.7	64.6±10.8	67.4±10.0
Printing and allied industries		80:2	233:44	82:13	51:15	213:55	136:15
	1316	67.1±9.4	64.8±11.7	66.9±10.5	67.1±10.5	64.5±11.5	67.1±11.0
Chemicals, and chemical and allied products		121:28	797:75	233:17	151:9	614:63	532:25
	3656	65.2±8.92	63.9±8.2	64.2±8.8	67.5±9.6	66.4±11.6	68.9±10.2
Petroleum and coal products		19:0	82:5	20:3	16:0	68:3	50:1
	360	66.7±10.3	61.5±11.8	68.0±10.5	58.0±15.9	63.4±10.9	64.9±8.6
Plastic produsts, except otherwise classified		32:3	95:38	30:1	19:5	92:38	71:18
	599	61.5±10.8	61.0±11.6	60.8±11.9	61.7±9.7	64.5±11.7	64.4±9.5
Rubber products		14:1	58:14	25:3	11:6	40:14	33:4
	316	61.3±12.1	63.1±11.3	61.6±10.5	66.8±10.1	66.6±11.9	67.5±10.9
Leather tannning, leather products and fur		1:0	23:6	11:1	4:4	11:4	9:5
	106	−	60.1±11.4	64.9±7.3	59.8±10.0	62.4±9.5	62.5±9.8
Ceramic, stone and clay products		88:1	441:70	159:23	77:14	323:56	378:34
	2167	66.9±9.5	64.5±11.6	64.9±11.9	67.4±11.4	67.1±10.4	67.9±9.4
Iron and steel		173:2	946:46	321:12	179:17	659:42	568:25
	3970	65.7±9.5	63.6±11.4	64.3±9.94	66.8±10.5	66.4±10.4	69.0±9.37
Non-ferrous metals and products		52:2	236:24	65:4	53:3	176:18	168:5
	1091	66.1±10.6	65.1±11.9	64.2±8.8	67.4±9.8	65.5±10.6	69.5±10.0
Fabricated metal products		223:9	1,015:193	307:31	178:44	750:203	598:68
	4614	65.8±8.9	65.0±8.5	64.9±10.2	67.8±9.3	66.4±10.1	68.3±9.75
General purpose machinery		156:4	889:90	281:12	152:23	682:97	524:47
	3992	66.4±8.3	64.3±11.7	64.3±10.2	66.9±10.3	64.8±11.4	67.9±11.0
Electrical machinery, equipment and supplies		55:3	262:81	65:14	49:13	258:66	169:43
	1497	66.2±10.5	61.9±11.9	60.7±11.8	63.7±10.3	63.8±11.7	64.9±11.3
Information and communication electronics		29:3	119:39	28:8	38:10	129:22	81:27
	783	65±9.3	60.6±12.7	62.4±11.6	61.5±12.4	62.8±12.8	65.7±11.1
Electronic parts, devices and electronic circuits		20:1	116:69	31:10	33:18	120:71	68:26
	837	64.6±14.5	56.6±11.6	61.5±11.1	61.7±9.1	58.6±11.9	62.7±10.6
Transportation equipment		140:6	852:58	281:7	160:20	550:96	562:44
	3666	66.9±9.2	65.2±11.7	64.9±10.0	67.1±11.2	66.0±11.2	67.33±10.5
Precision machinery		21:0	96:19	38:2	21:2	76:25	49:10
	487	68.9±12.2	60.4±13.3	62.5±8.2	64.1±12.6	62.7±10.0	64.4±9.9
Miscellaneous manufacturing industries		31:1	180:80	46:6	24:11	144:60	90:28
	952	6.9±9.4	66.9±11.2	66.9±11.2	67.3±12.5	66.4±10.4	68:9±10.7

表6. Odds ratio for each manufacturing industry using all cases

Industrial category		Prostate	Breast	Kidney	Ureter	Bladder
	Number of cases	2,769	2,462	1,149	494	3,639
Food (reference)						
	3,570					
Beverages, tobacco and feed		1.27(0.87−1.86)	1.18(0.82−1.71)	1.07(0.61−1.91)	1.73(0.83−3.62)	1.01(0.71−1.43)
	612	0.207	0.359	0.802	0.145	0.966
Textile mill products		1.10(0.78−1.57)	1.09(0.82−1.55)	1.52(0.98−2.35)	1.90(1.03−3.51)	1.03(0.77−1.39)
	1,022	0.583	0.562	0.057	0.040†	0.827
Clothes and other textiles		1.22(0.83−1.79)	1.22(1.04−1.44)	1.21(0.81−1.80)	1.70(0.96−3.00)	1.04(0.79−1.36)
	1,721	0.300	0.016†	0.355	0.067	0.801
Lumber and wood products, except furniture		0.69(0.51−0.93)	0.82(0.59−1.12)	0.92(0.62−1.38)	1.18(0.65−2.09)	0.69(0.54−0.89)
	1,319	0.014†	0.220	0.698	0.581	0.005‡
Furniture and fixtures		1.16(0.82−1.64)	1.34(0.84−2.15)	1.42(0.87−2.32)	1.76(0.88−3.51)	0.94(0.68−1.31)
	652	0.400	0.219	0.164	0.112	0.731
Pulp, paper and paper products		1.19(0.87−1.62)	1.05(0.76−1.44)	1.23(0.79−1.89)	0.55(0.24−1.27)	0.93(0.69−1.21)
	1,065	0.266	0.772	0.355	0.162	0.524
Printing and allied industries		1.16(0.85−1.58)	1.30(0.99−1.69)	1.63(1.09−2.43)	2.01(1.15−3.52)	1.41(1.09−1.81)
	1,316	0.353	0.053	0.016†	0.014†	0.008‡
Chemicals, and chemical and allied products		1.26(1.01−1.57)	1.26(1.01−1.58)	1.40(1.03−1.91)	0.97(0.59−1.58)	1.03(0.85−1.25)
	3,656	0.040†	0.04†	0.030†	0.909	0.795
Petroleum and coal products		1.83(1.16−2.89)	1.14(0.48−2.72)	1.94(1.02−3.69)	1.01(0.29−3.45)	1.58(1.04−2.41)
	360	0.009‡	0.770	0.045†	0.982	0.032†
Plastic products, except otherwise classified		0.76(0.48−1.18)	1.37(0.99−1.88)	1.41(0.85−2.35)	0.77(0.29−2.00)	0.79(0.54−1.15)
	599	0.218	0.050	0.189	0.586	0.216
Rubber products		0.92(0.52−1.63)	1.33(0.79−2.22)	1.74(0.89−3.39)	2.82(1.19−6.70)	1.33(0.86−2.06)
	316	0.779	0.278	0.102	0.018†	0.196
Leather tannning, leather products and fur		1.81(0.56−5.85)	1.38(0.64−2.95)	1.99(0.58−6.81)	2.41(0.30−19.28)	1.95(0.79−4.81)
	106	0.319	0.406	0.274	0.407	0.143
Ceramic, stone and clay products		0.87(0.66−1.13)	0.95(0.72−1.25)	0.93(0.64−1.36)	1.35(0.80−2.26)	1.02(0.82−1.26)
	2,167	0.286	0.704	0.720	0.260	0.875
Iron and steel		1.19(0.95−1.47)	1.11(0.84−1.47)	1.15(0.84−1.56)	1.30(0.82−2.08)	1.08(0.89−1.30)
	3,970	0.126	0.473	0.387	0.266	0.423
Non−ferrous metals and products		1.18(0.87−1.61)	1.95(1.29−2.92)	1.18(0.89−2.14)	1.25(0.64−2.43)	1.28(0.98−1.67)
	1,091	0.288	0.001‡	0.149	0.520	0.063
Fabricated metal products		0.76(0.61−0.94)	0.81(0.67−0.98)	0.83(0.61−1.13)	0.78(0.49−1.24)	0.74(0.62−0.89)
	4,614	0.013†	0.030†	0.236	0.290	0.002‡
General−purpose mechinery		1.04(0.83−1.29)	1.14(0.92−1.41)	1.34(0.99−1.80)	1.29(0.81−2.02)	1.04(0.86−1.25)
	3,992	0.726	0.237	0.055	0.286	0.675
Electrical machinery, equipment and supplies		1.60(1.19−2.16)	1.27(0.98−1.63)	2.49(1.75−3.55)	2.09(1.18−3.70)	1.46(1.13−1.88)
	1,497	0.002‡	0.069	0.000‡	0.011†	0.003‡
Information and communication electronics		1.81(1.27−2.58)	1.48(1.10−1.98)	2.69(1.77−4.11)	2.14(1.02−4.45)	1.69(1.23−2.32)
	783	0.001‡	0.009‡	0.000‡	0.043†	0.001‡
Electronic parts, devices and electronic circuits		1.06(0.62−1.58)	1.13(0.88−1.45)	2.07(1.37−3.13)	1.75(0.86−3.53)	1.26(0.93−1.72)
	837	0.765	0.329	0.001‡	0.120	0.136
Transportation equipment		0.89(0.71−1.11)	0.99(0.78−1.27)	1.03(0.75−1.41)	1.41(0.89−2.22)	1.03(0.85−1.25)
	3,666	0.302	0.961	0.873	0.140	0.746
Precision machinery		0.92(0.58−1.44)	1.52(1.04−2.21)	1.16(0.62−2.17)	0.21(0.03−1.59)	1.11(0.76−1.62)
	487	0.703	0.961	0.652	0.132	0.593
Miscellaneous manufacturing industries		0.78(0.53−1.15)	1.20(0.92−1.58)	1.17(0.73−1.87)	1.57(0.82−2.99)	1.06(0.79−1.42)
	952	0.209	0.185	0.516	0.176	0.686

Odds ratios of a total of 40,370 cases were estimated by logistic regression. The model included age, sex, period of admission, admission hospital, smoking (Brinkman Index), and consumption of alcohol as covariates.

Each upper row shows the odds ratio (95% confidence interval) using food manufacturing as a reference (ref).

Each lower row shows *p*−values <0.01‡ or <0.05† that were considered to be statistically significant.

表6.（*continued.*）

Industrial category	Number of cases	Esophagus	Stomach	Liver	Pancreas	Colon	Lung
	Number of cases	1,730	9,741	2,869	1,944	7,758	5,815
Food（reference）							
	3,570						
Beverages, tobacco and feed		1.02(0.67−1.54)	0.95(0.75−1.20)	0.96(0.68−1.37)	1.12(0.76−1.65)	1.01(0.86−1.40)	0.80(0.59−1.09)
	612	0.932	0.686	0.834	0.562	0.446	0.163
Textile mill products		1.03(0.71−1.49)	0.98(0.81−1.19)	1.16(0.87−1.54)	1.05(0.76−1.45)	1.00(0.81−1.24)	1.04(0.82−1.14)
	1,022	0.873	0.803	0.300	0.779	0.978	0.765
Clothes and other textiles		0.79(0.54−1.16)	1.02(0.87−1.19)	1.04(0.804−1.35)	0.98(0.75−1.29)	1.11(0.95−1.29)	1.06(0.86−1.29)
	1,721	0.237	0.803	0.766	0.884	0.191	0.596
Lumber and wood products, except furniture		0.54(0.39−0.75)	0.73(0.62−0.86)	0.51(0.38−0.67)	0.67(0.49−0.91)	0.74(0.61−0.88)	0.83(0.68−1.02)
	1,319	0.000‡	0.000‡	0.000‡	0.010†	0.001‡	0.072
Furniture and fixtures		0.56(0.35−0.89)	0.92(0.73−1.15)	0.64(0.44−0.93)	0.61(0.38−0.97)	1.16(0.92−1.46)	0.89(0.67−1.19)
	652	0.014†	0.454	0.018†	0.037†	0.223	0.437
Pulp, paper and paper products		0.75(0.53−1.06)	0.97(0.81−1.16)	0.82(0.61−1.09)	0.83(0.59−1.16)	1.05(0.86−1.27)	0.89(0.70−1.12)
	1,065	0.107	0.724	0.182	0.290	0.639	0.312
Printing and allied industries		1.26(0.92−1.71)	1.03(0.86−1.22)	1.03(0.78−1.36)	1.16(0.85−1.57)	1.37(1.15−1.64)	1.00(0.79−1.25)
	1,316	0.148	0.766	0.838	0.351	0.000‡	0.997
Chemicals, and chemical and allied products		0.67(0.52−0.87)	1.06(0.93−1.19)	0.87(0.71−1.06)	0.87(0.69−1.09)	1.13(0.98−1.29)	1.07(0.91−1.25)
	3,656	0.002‡	0.398	0.174	0.234	0.086	0.411
Petroleum and coal products		1.15(0.67−1.98)	1.47(1.09−1.98)	1.07(0.66−1.73)	1.16(0.65−2.05)	1.56(1.14−2.16)	1.51(1.04−2.18)
	360	0.605	0.011‡	0.787	0.612	0.006‡	0.029†
Plastic products, except otherwise classified		1.04(0.69−1.57)	0.92(0.74−1.16)	0.67(0.45−1.00)	0.75(0.48−1.17)	1.09(0.87−1.39)	1.07(0.81−1.41)
	599	0.835	0.485	0.054	0.204	0.446	0.623
Rubber products		1.02(0.56−1.83)	1.11(0.81−1.52)	1.27(0.81−1.99)	1.19(0.69−2.04)	1.08(0.76−1.52)	0.94(0.62−1.42)
	316	0.949	0.503	0.294	0.535	0.680	0.767
Leather tannning, leather products and fur		0.36(0.05−2.89)	1.89(1.13−3.17)	2.36(1.15−4.83)	2.85(1.26−6.47)	1.45(0.77−2.80)	2.00(1.01−3.99)
	106	0.341	0.015†	0.019‡	0.012‡	0.243	0.028†
Ceramic, stone and clay products		0.65(0.48−0.86)	0.94(0.82−1.08)	0.97(0.78−1.21)	0.78(0.59−1.02)	0.95(0.82−1.11)	1.26(1.06−1.49)
	2,167	0.003‡	0.400	0.771	0.075	0.538	0.008‡
Iron and steel		0.71(0.56−0.91)	1.03(0.91−1.16)	0.94(0.79−1.14)	0.98(0.79−1.23)	1.07(0.96−1.43)	1.04(0.89−1.21)
	3,970	0.006‡	0.213	0.540	0.898	0.294	0.615
Non−ferrous metals and products		0.88(0.62−1.24)	1.12(0.94−1.35)	0.89(0.66−1.21)	1.15(0.83−1.59)	1.17(0.96−1.43)	1.18(0.91−1.43)
	1,091	0.459	0.213	0.488	0.410	0.110	0.267
Fabricated metal products		0.72(0.57−0.90)	0.91(0.81−1.02)	0.77(0.63−0.92)	0.78(0.63−0.96)	0.95(0.85−1.08)	0.83(0.71−0.96)
	4,614	0.004‡	0.096	0.005‡	0.017†	0.439	0.011†
General−purpose mechinery		0.64(0.49−0.81)	0.99(0.88−1.12)	0.86(0.71−1.04)	0.84(0.67−1.04)	1.10(0.97−1.25)	0.97(0.83−1.13)
	3,992	0.000‡	0.953	0.135	0.120	0.126	0.709
Electrical machinery, equipment and supplies		0.98(0.70−1.38)	1.37(1.16−1.61)	1.00(0.75−1.33)	1.15(0.85−1.57)	1.67(1.41−1.97)	1.56(1.27−1.92)
	1,497	0.917	0.000‡	0.991	0.368	0.000‡	0.000‡
Information and communication electronics		1.11(0.73−1.69)	1.21(0.98−1.49)	0.87(0.59−1.27)	1.79(1.27−2.54)	1.46(1.78−1.81)	1.60(1.24−2.07)
	783	0.616	0.082	0.467	0.001‡	0.001‡	0.000‡
Electronic parts, devices and electronic circuits		0.59(0.36−0.95)	1.15(0.95−1.39)	0.83(0.58−1.18)	1.39(0.99−1.93)	1.43(1.18−1.73)	1.13(0.88−1.46)
	837	0.030†	0.139	0.290	0.051	0.001‡	0.344
Transportation equipment		0.61(0.47−0.78)	0.94(0.83−1.05)	0.85(0.70−1.60)	0.91(0.73−1.34)	0.97(0.85−1.11)	1.11(0.95−1.29)
	3,666	0.000‡	0.295	0.627	0.398	0.644	0.174
Precision machinery		0.75(0.45−1.25)	1.14(0.89−1.46)	1.09(0.75−1.60)	1.00(0.63−1.60)	1.30(1.01−1.69)	0.98(0.70−1.36)
	487	0.269	0.314	0.627	0.987	0.043†	0.894
Miscellaneous manufacturing industries		0.63(0.41−0.95)	1.13(0.94−1.35)	0.70(0.51−0.98)	0.65(0.45−0.96)	1.15(0.94−1.39)	0.87(0.68−1.12)
	952	0.031‡	0.199	0.039†	0.031†	0.177	0.299

III. 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
Zaitsu M, Cuevas AG, Trudel-Fitzgerald C, Takeuchi T, Kobayashi Y, Kawachi I	Occupational class and risk of renal cell cancer	Health Science Reports	1: e49	https://doi.org/10.1002/hsr2.49	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
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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

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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]

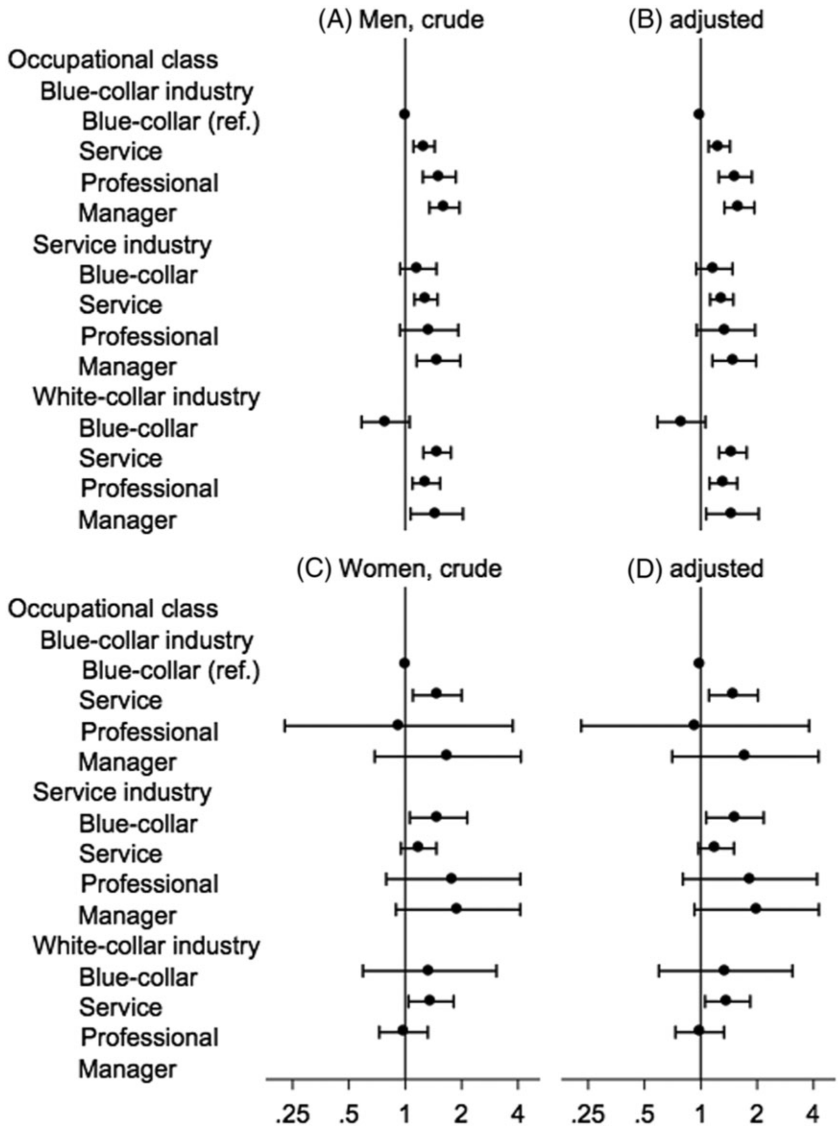

FIGURE 2 Odds ratios for renal cell cancer across different occupational classes stratified by sex. The odds ratio (dot) and 95% confidence interval (bar) were estimated by unconditional logistic regression with 5 imputed data. Male and female odds ratios were (A, C) adjusted for age and year of admission 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

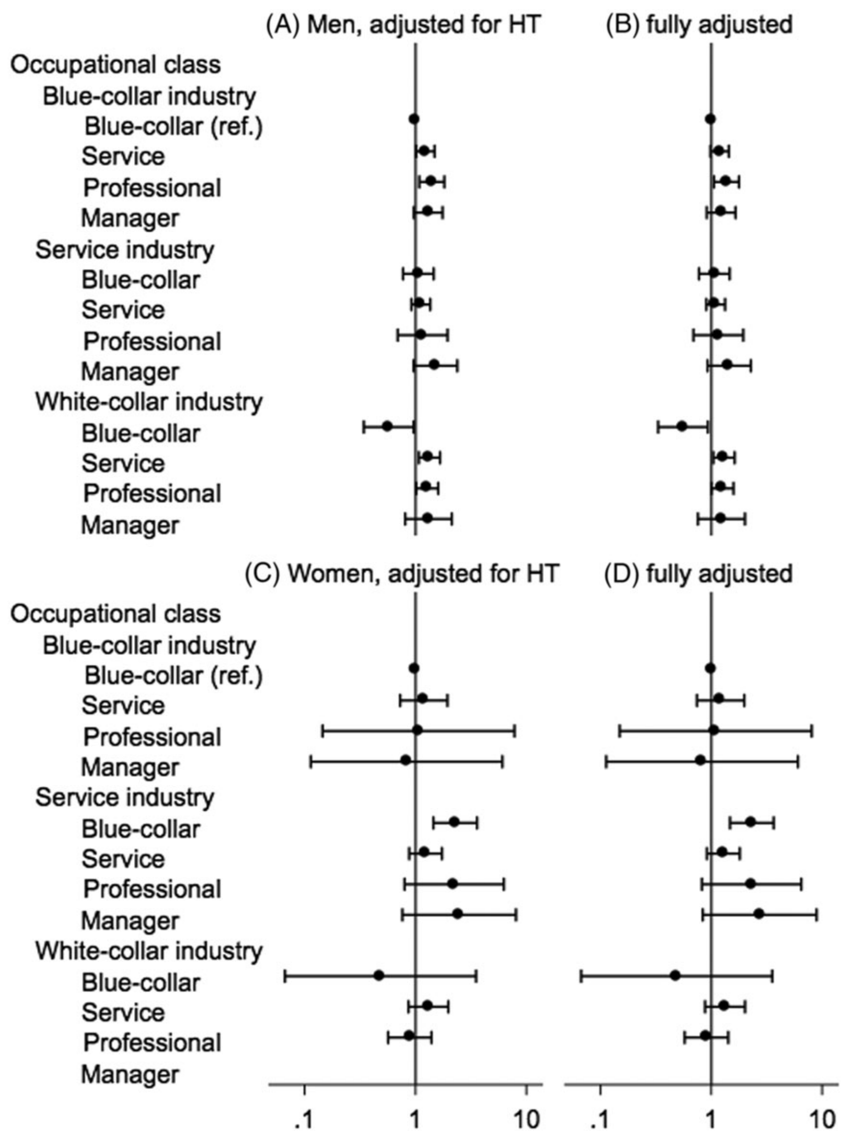

FIGURE 3 Odds ratios adjusted for hypertension and other stress-related factors in a subset data after 2005. The odds ratio (dot) and 95% confidence interval (bar) were estimated by unconditional logistic regression with 5 imputed data. Male and female odds ratios were (A, C) adjusted for age, year of 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

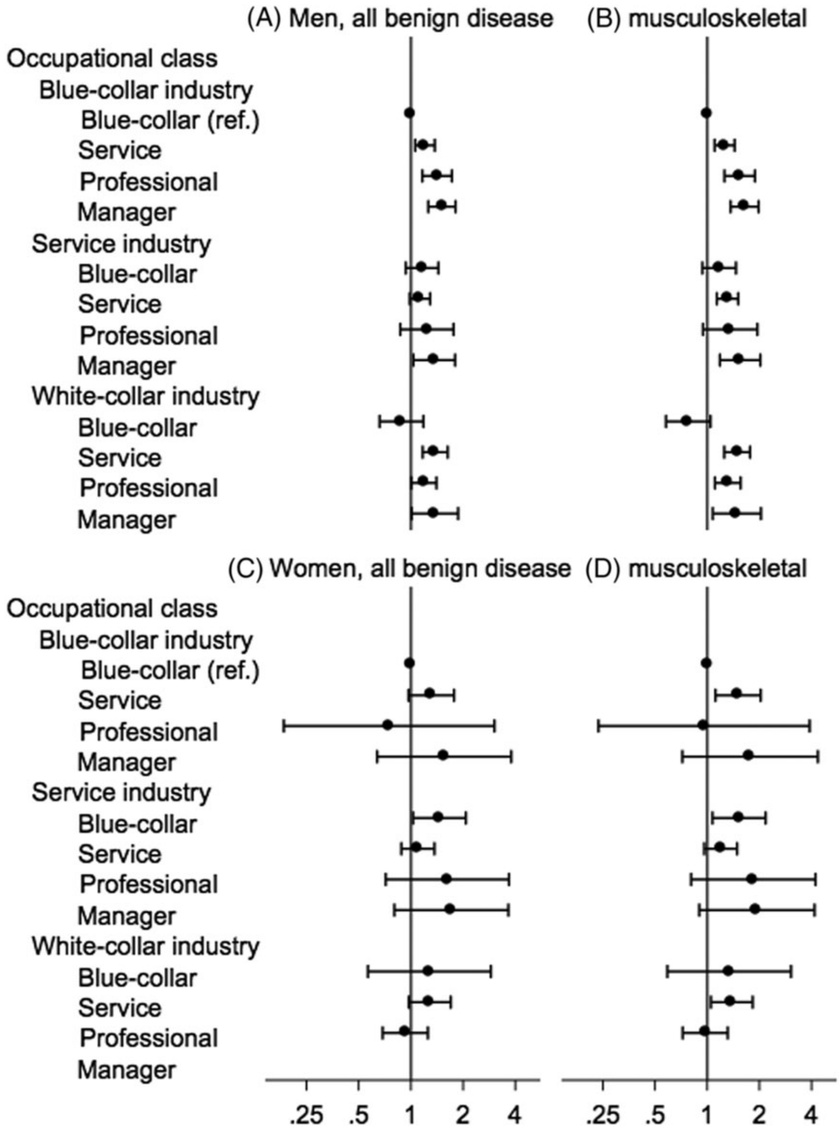

FIGURE 4 Sensitivity analysis with alternative control groups. The odds ratio (dot) and 95% confidence interval (bar) were estimated by unconditional logistic regression, adjusted for age and year of admission with 5 imputed data. Male and female control groups were, respectively, (A, C) patients diagnosed 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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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).

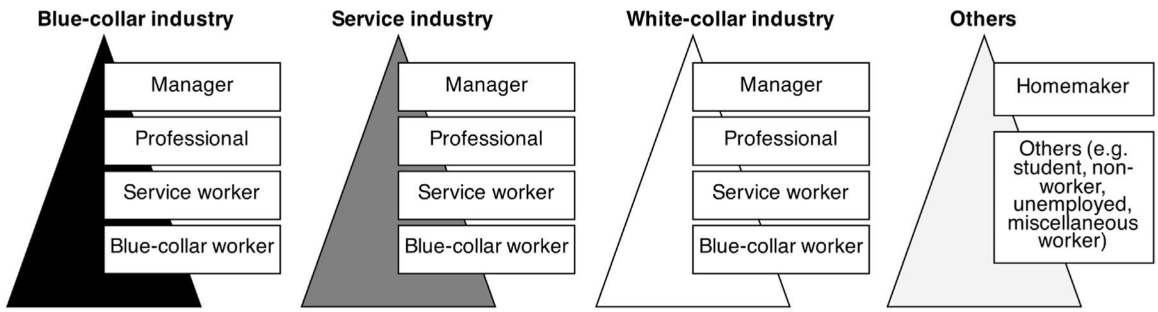
The cancer cases were those patients whose main diagnoses were cancer, confirmed by physicians on discharge, for the first-time stay in the hospitals for the initial cancer, together with pathological or imaging information (e.g., computed tomography, magnetic resonance imaging, and endoscopy); they 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

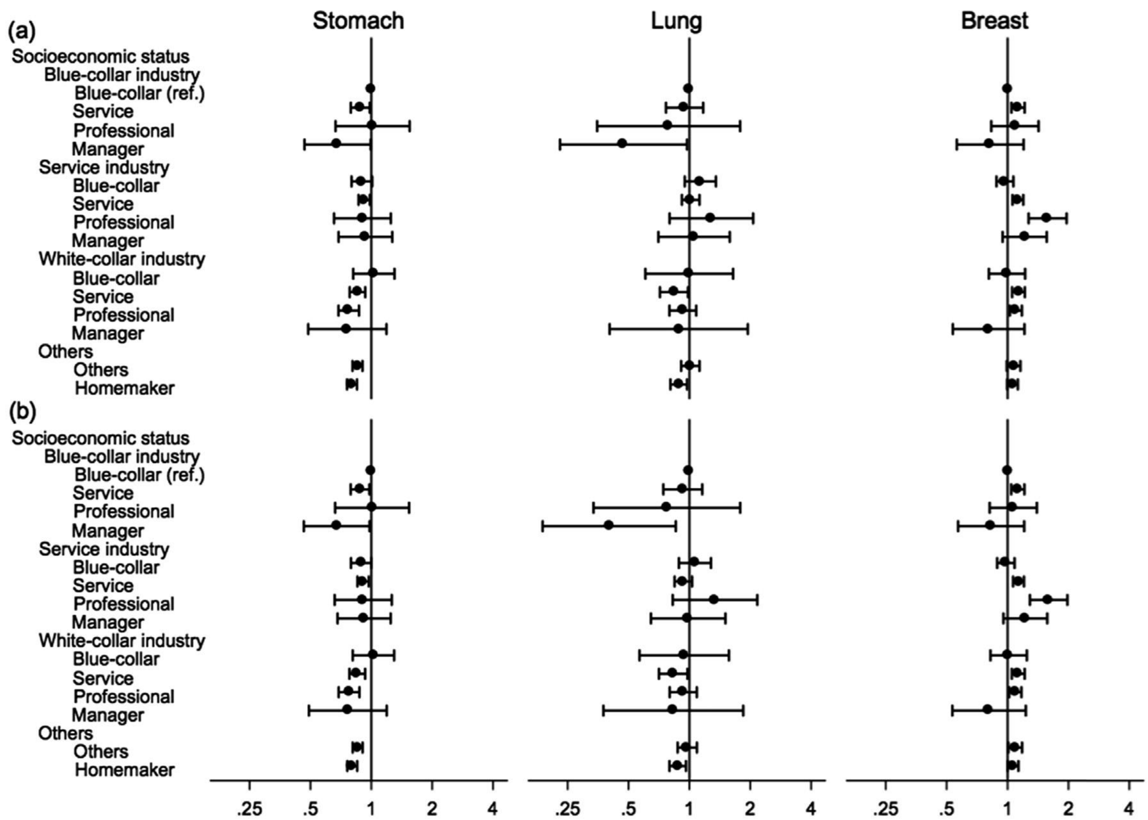


Fig. 2. Socioeconomic gradients associated with risk for incidence of stomach, lung, and breast cancers. The odds ratio (dot) and 95% confidence interval (bar) were estimated by conditional logistic regression, (a) matched for age, admission date, and admitting hospital and (b) additionally adjusted 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

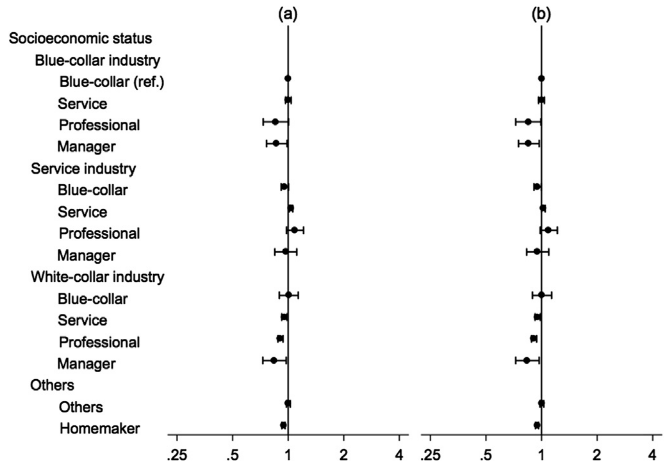


Fig. 3. Socioeconomic gradient associated with risk for overall female cancer incidence. The odds ratio (dot) and 95% confidence interval (bar) were estimated by conditional logistic regression, (a) matched for age, admission date, and admitting hospital and (b) additionally adjusted for smoking and 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 over-diagnosis, 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

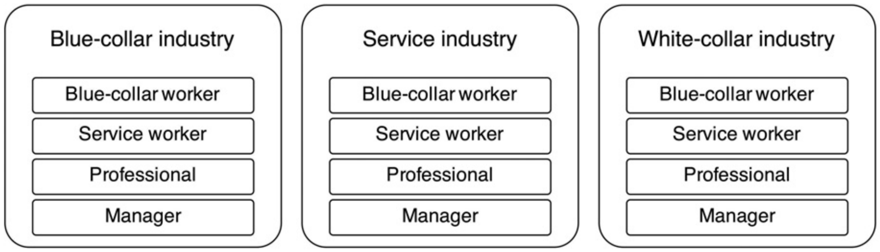
Study Setting

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).

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Table 3. Background Characteristics Between Cases and Controls

Characteristics*	n (%) or Mean (SD)		
	Control (n=999 976)	Case (n=128 615)	*P* Value†
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.

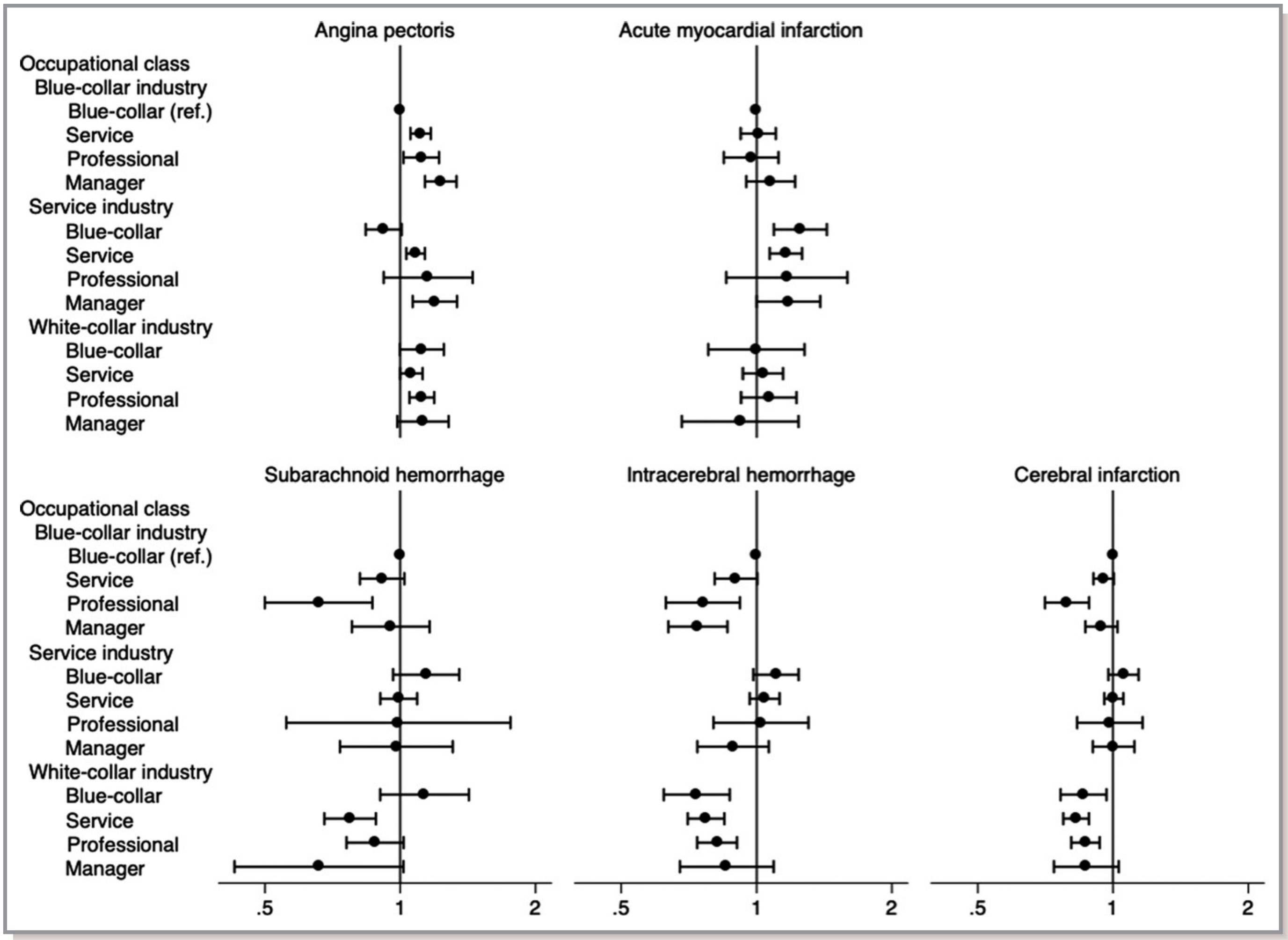

Figure 3. Odds ratios associated with occupational class for incidence of angina pectoris, acute myocardial infarction, subarachnoid hemorrhage, intracerebral hemorrhage, and cerebral infarction. The odds ratio (dot) and 95% CI (bar) were estimated by conditional logistic regression with multiple imputation, 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

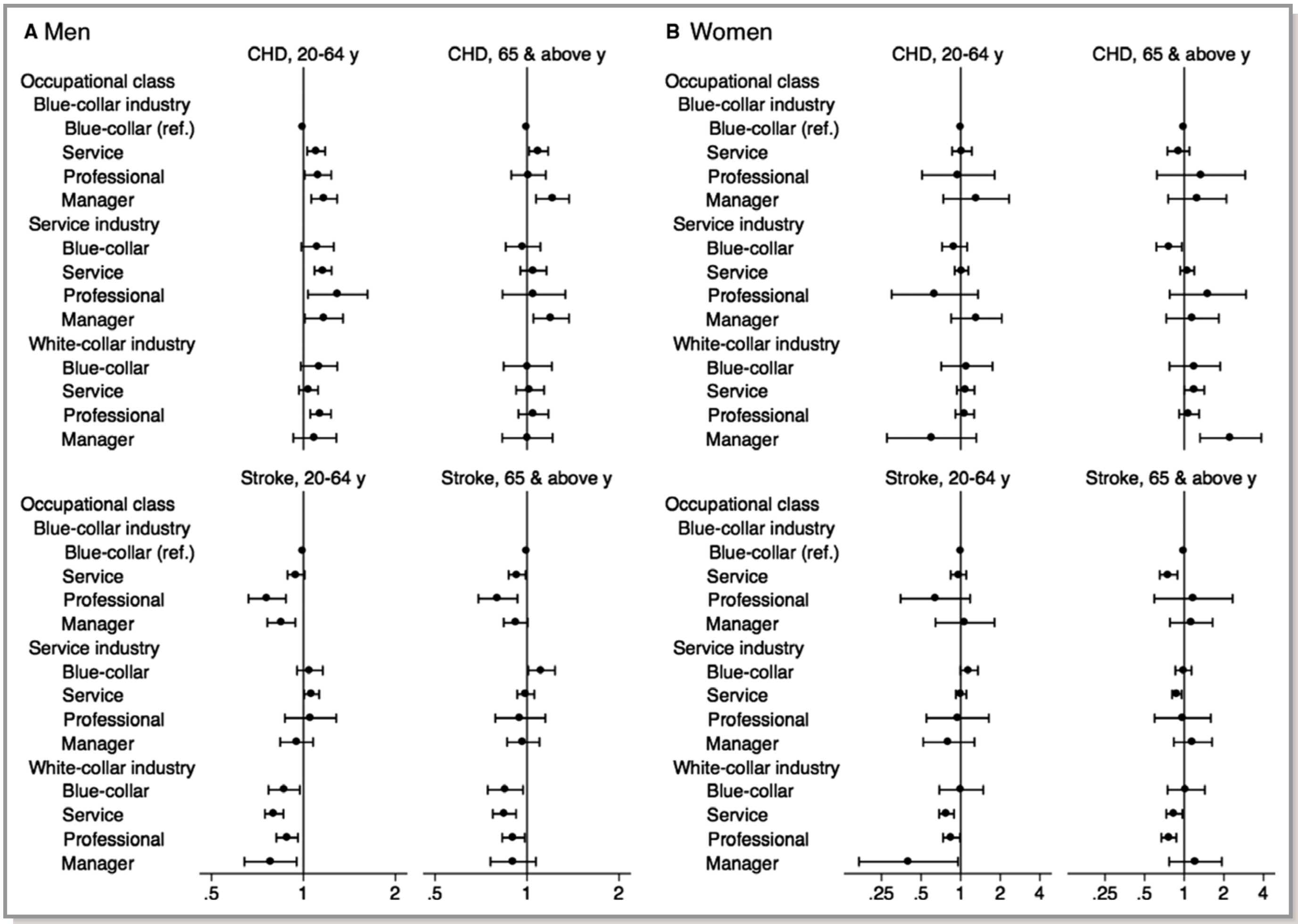

Figure 4. Occupational class gradients stratified by sex and age. The odds ratio (dot) and 95% CI (bar) were estimated by conditional logistic regression with multiple imputation, matched for age, admission date, and admitting hospital, additionally adjusted for smoking and alcohol consumption. The numbers 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

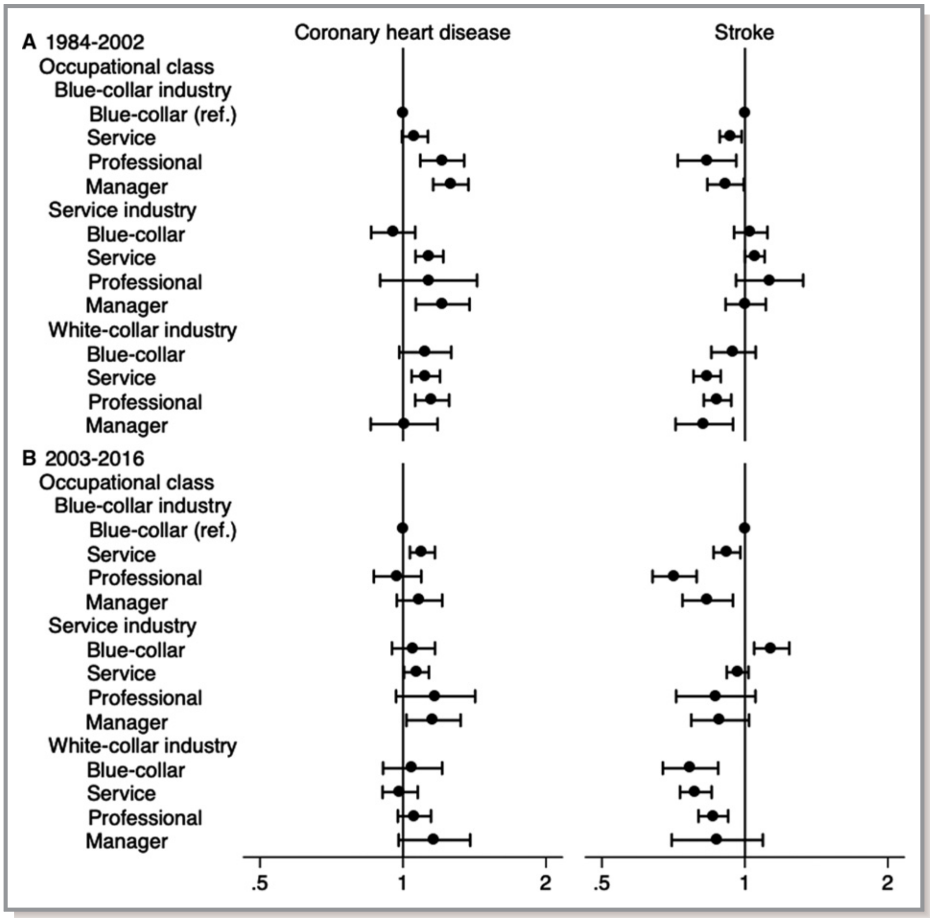

Figure 5. Occupational class gradients stratified by admission period. The odds ratio (dot) and 95% CI (bar) were estimated by conditional logistic regression with multiple imputation, matched for age, admission date, and admitting hospital, additionally adjusted for smoking and alcohol consumption. 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,

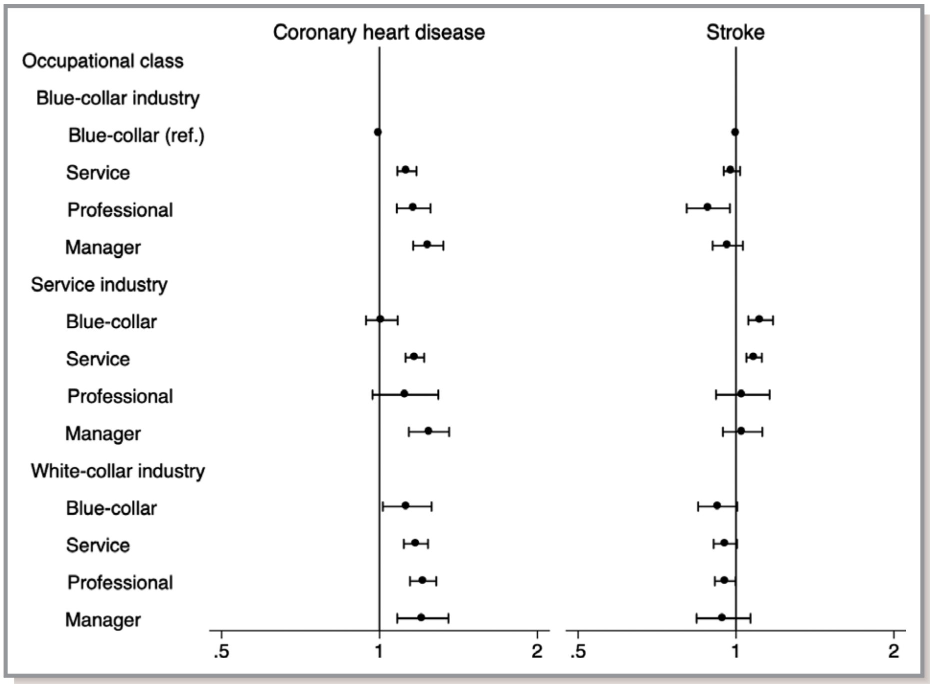

Figure 6. Odds ratio in each occupational class for coronary heart disease and stroke incidence estimated with alternative control groups. The odds ratio (dot) and 95% CI (bar) were estimated by conditional logistic regression with multiple imputation, matched for age, admission date, and admitting hospital, 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

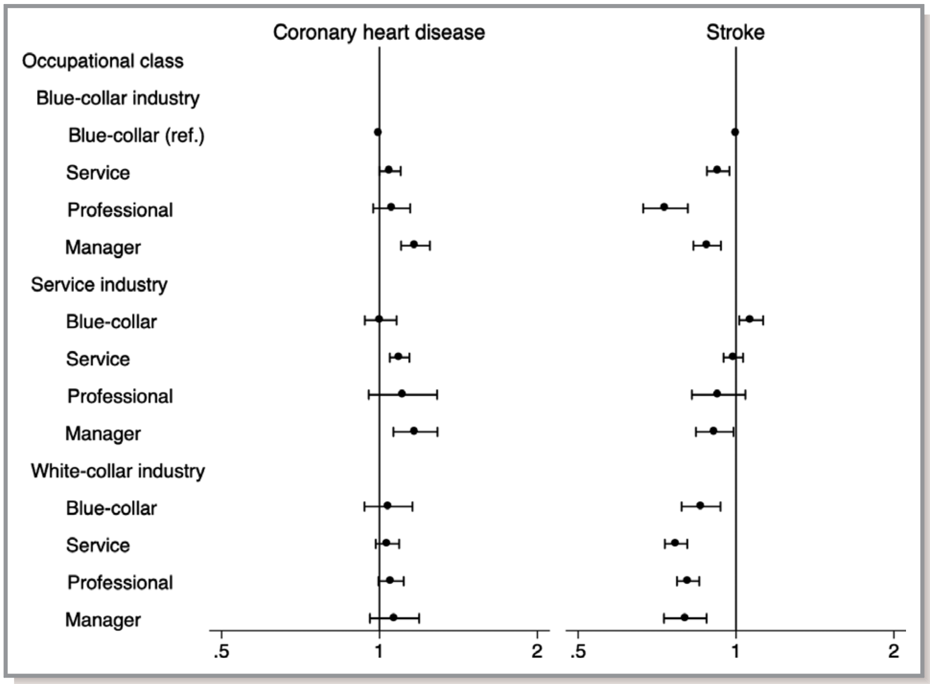

Figure 7. Risks of coronary heart disease and stroke incidence associated with most recent occupational class. The odds ratio (dot) and 95% CI (bar) were estimated by conditional logistic regression with multiple imputation, matched for age, admission date, and admitting hospital, additionally adjusted 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

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	1.05 (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

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