労災疾病臨床研究事業費補助金

化学物質の有害性評価を加速するための国内疫学的サーベイランス手法の開発

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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。がんについての解析は前々年度、前年度実施した。本年度はがん以外の疾病として循環器疾患を対象にした網羅的解析や化学物質曝露機会の多い製造業に焦点をあてた分析などを実施した。

大規模医療データとして主に用いたのは、独立行政法人労働者健康安全機構が保有する約 690 万件の入院患者病職歴調査データベース（病職歴調査データベース）である。本研究では、上記データベースの最長職業を取り上げ、日本標準職業分類 JSOC および日本標準産業分類 JSIC を基に 4 つの職業（ブルーカラー職、サービス職、専門職、管理職）、3 つの産業（ブルーカラー産業、サービス産業、ホワイトカラー産業）に分類し、がん以外の疾患として、死因の上位である循環器疾患（心血管疾患、脳血管疾患）との関連を網羅的に分析した。また、同様の目的のデータベースの比較参考例として、海外の病職歴データベースについて文献調査を行った。分担研究においては、ICOD-R の一部対象者についてカルテ（診療録）レビューや病理診断記録の確認などを行うとともに、有害物質曝露による発がんの病因論検討を行った。

本研究により、大規模データベースから標準化された職業分類と産業分類の双方を用いて、職業と循環器疾患との関連を網羅的に検討する方法が開発された。その方法を ICOD-R に適用した結果、職業は循環器疾患の罹患リスクと関連することが示された。とりわけ、我が国の専門職/管理職では心血管疾患の罹患リスクが高く、脳血管疾患のリスクが相対的に低いという可能性が示唆された。分担研究では、化学物質曝露機会の多い製造業に限定した詳細な分析から、製造業種内でのがん罹患リスクの差の可能性が示唆され、オッズ比の高い業種の症例については、カルテレビューや病理診断記録の確認などを行った。入手可能であった病歴要約のうち、病理組織学的に癌の診断を確認できたものは 90%近くに達した。北欧諸国における国勢調査・住民登録とがん登録をリンケージしたデータベース（NOCCA）は、職業・職種によるがんの超過発生、超過死亡に即応した精度の高い研究を可能としており、我が国での可能性について検討する必要があると考えられた。

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A. 研究目的

日本では、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。我々がこれまでに行ってきた研究により、幅広い職業・産業から化学物質等に対する曝露を網羅的に探索し、がん罹患のリスクの関係の状況を把握する手法が開発された（Zaitsu M, 2018a, 2018b, 2019）。この先行研究では、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が、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。しかし、がんに次ぐ死因第 2 位である循環器疾患の罹患リスクと職業・産業の関係の状況を把握する手法は開発されていない。

そこで、本年度の研究では、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、幅広い職業および産業分類を，先行研究（Zaitsu M, 2018a, 2018b, 2019）で用いた職業・産業グループに分類し、職業と循環器疾患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。

さらに、比較参考例として、海外の病職歴データベースについて文献調査を行った。

分担研究においては、ICOD-R の一部対象者についてカルテ（診療録）レビューや病理診断記録の確認などを行うとともに、有害物質曝露による発がんの病因論検討を行った。

B. 研究方法

データセッティング

独立行政法人労働者健康安全機構が保有する約 600 万件の ICOD-R データを用いて、hospital-based case-control study を実施した。ICOD-R の詳細については先行研究（Zaitsu M, 2018a, 2018b, 2019）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（https://www.research.johas.go.jp）を参照されたい。ICOD-R は全国の労災病院に入院した全入院患者の病歴および職業歴を抽出したデータであり、独立行政法人労働者健康安全機構が 1984 年からデータベース化を行っている。このデータベースには、各患者の性・年齢等の基本的背景、退院時の主病名、並存疾患名の他に、喫煙、飲酒の生活習慣行動がある。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。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。

症例 case と対照 control

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

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

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

説明変数：網羅的な職業分類

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ため、先行研究のアルゴリズム（Zaitsu M, 2018a, 2018b, 2019）により、これらから最長職業を抽出し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、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）に分類した（Zaitsu M, 2018a, 2018b, 2019）。学生、無職、退職者、主婦等の被雇用者でない者は除外した。最長職業に従事した平均年数は 27 年であり、従事期間と循環器疾患のリスクに有意な関連は見られなかった。

共変量

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

統計解析

解析対象者のうち、合わせて 20%について、職業、喫煙、飲酒の情報いずれかが欠損していた。具体的には、職業 6.0%、喫煙 9.5%、飲酒 18.6%であった。データ欠損群を除外して解析することはデータ解釈にバイアスを生じる可能性があるため（表 2）、先行研究（Zaitsu M, 2018a, 2018b, 2019）に基づき、解

析対象者 1,128,591 名の全データを利用して Multiple Imputation by Chain Method（MICE）法による多重補完 multiple imputation を実施し、数学的に欠損値を予測し代入したデータセットを 5 セット作成し統合して解析した。この統合したデータセットを用いて、各職業の循環器疾患のオッズ比（OR）と 95%信頼区間（CI）を算出した。Reference はブルーカラー産業のブルーカラー職とした。メインの統計解析モデルは、年齢、病院、入院施設、入院年をマッチさせた条件付きロジスティック回帰分析を用いた（model 1）。次に、喫煙と飲酒を調整したオッズも求めた（model 2）。統計学的有意水準は両側 0.05％とした。統計解析には、STATA/MP13.1（ StataCorp LP, College Station, Texas）を使用した。

予備的追加実験

さらに、職業と循環器疾患の関連の媒介に関わる可能性のある慢性炎症について、組織中の炎症性バイオマーカーである high mobility group box 1（HMGB1）に注目し、予備的な追加実験として関東労災病院に保存されている腎細胞がん 91 検体の病理組織をホワイトカラー職種（50 検体）とそれ以外の職種（41 検体）に分けて、HMGB1 の免疫染色を追加で行った。

海外の病職歴データベース

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

（倫理面への配慮）

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

C. 研究結果

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

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

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

また、予備的な追加実験では、HMGB1 の

腎細胞がんにおける染色パターンは、ホワイトカラー職で 50%が陽性、ホワイトカラー職以外では 46%が陽性となり、統計学的な有意差は見られなかった（カイ 2 乗検定, P=0.83）。

海外の病職歴データベース

Nordic Occupational Cancer (NOCCA) project は、1943 年にデンマークで開始された全国がん登録に発する。その後、1953 年にフィンランドとノルウェー、1955 年にアイスランド、1958 年にスウェーデンで全国がん登録が開始された。さらに、スウェーデンにおいて、国勢調査（1960 年実施）とがん登録の個人ベースのリンケージが最初に行われ、その後、各国が追随した。職業分類も 5 カ国間で標準化が行われた（Pukkala E, et al, 2009）。最近では、従来型の数年毎実施の国勢調査を廃止し、社会保障番号や現職などと紐付けされ電子化された住民登録データ（computerised central population registries）とのリンケージを行っている国もある。同プロジェクトによれば、男女のがんの約 5%が仕事（職業）と関連し、男性のがんの約 35%、女性のがんの約 16%が社会経済階層と関連しているとされる（Pukkala E, 2015）。職業・産業による種々のがんの標準化罹患比（standardised incidence ratios）を推定している（資料 1）（Pukkala E, et al, 2009）。また、日本の印刷業者における 1.2.ジクロロプロパンによる胆管がん発生の報告に対応して、印刷業従事者に関して NOCCA データベースを用いた後ろ向きコホート研究が実施されている（Vlaanderen J, et al, 2013）。

D. 考察

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

欧米諸国では、循環器疾患の社会格差については最近のレビューでも結論づけられ、循環器疾患のリスクは職業階層のような社会経済学的要因と非常に強い結びつきがあり、社会経済学的に有利な人ほど（例えば専門職や管理職従事者）循環器疾患のリスクが低くなるとされる。しかし、この循環器疾患の罹患リスクの「勾配」は、歴史上不変であったわけではない。20 世紀前半には、冠動脈疾患は「executive coronary」という用語で描写されるように、豊かさによる疾患として認識されていた（Kawachi I, 1998; Osler W, 1910）。しかし 20 世紀の間にはこの勾配は逆転した。これは、冠動脈疾患のリスクに対する理解が浸透したこと（禁煙、定期的な運動、食事、高血圧や脂質異常症の治療など）、および社会経済的に有利な人ほど健康的な生活習慣をより迅速に取り入れたことを反映している（Kawachi I, 1998）。

しかし、今回の我々の報告は、この歴史的なリスクの推移には必ずしも一致しない。

欧米諸国の趨勢に照らし合わせれば、日本の喫煙率や適量以上の飲酒率は、専門職/管理職でも依然として高い。また、本研究では、喫煙や飲酒によって循環器疾患の罹患リスクの職業による差を完全には説明できなかったことから、喫煙や飲酒以外の生活習慣と関連する職業による循環器疾患のリスクファクター、例えば不十分な身体活動量、高血圧、糖尿病や肥満などの関与が考えられる。近隣のアジア諸国でも、専門職/管理職などの職種でメタボリック症候群が多いことが報告されており、また、管理職の長時間労働などの関与も考えられる。特に日本のサービス産業の従業者は、顧客ニーズを満足させることが過度に期待されているため、長時間労働や職場ストレスの高さの関与が推定される。これらの関与の解明は今後の課題である。

一方、脳卒中については専門職や管理職従事者でリスクが低いこと示唆された。職業格差が冠動脈疾患と脳卒中で異なるということは、共通する主要なリスクファクター（喫煙や高血圧）があるものの、その他に、別々の要因があることも考えられる。例えば、幼少期の社会経済的要因などは、慢性血管炎症を惹起する可能性のある環境要因（Helicobacter pylori 感染症など）と関連があり、慢性血管炎症は脳卒中の罹患を増加させる。予備的な追加実験では、対象疾患が腎癌ではあるものの、慢性炎症の一つの指標である HMGB1 に関しては、局所的な差は検出できなかった。しかし、今回の我々が行ったように、国内の大規模な既存データを用いて、化学物質等の有害性や種々の職業上のリスク要因について、網羅的・疫学的に評価し、さらに biological pathway を解明していく手法はこれまで国内にはほとんど見られなかった。さらに、職業と循環器疾患の関連について、ストレスや環境因子、慢性炎症などの biological pathway を組み込んだ研究もほとんどないことから、今後のこの分野のさらなる研究が期待される。

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

なお、分担研究においては、化学物質曝

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

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

E. 結論

本研究により、大規模データベースから標準化された職業分類と産業分類の双方を用いて、職業とがん、および循環器疾患との関連を網羅的に検討する方法が開発された。本年度は循環器疾患について適用した結果、職業は循環器疾患の罹患リスクと関連することが示された。とりわけ、我が国の専門職/管理職では心血管疾患の罹患リスクが高く、脳血管疾患のリスクが相対的に低いという可能性が示唆された。分担研究では、化学物質曝露機会の多い製造業に限定した詳細な分析から、製造業種内でのがん罹患リスクの差の可能性が示唆されている。北欧諸国における国勢調査・住民登録とがん登録をリンケージしたデータベース（NOCCA）は、職業・職種によるがんの超過発生、超過死亡に即応した精度の高い研究を可能としており、我が国での可能性について検討する必要があると考えられた。

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F. 健康危険情報

なし

G. 研究発表

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2. 学会発表

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H. 知的財産権の出願・登録

なし

表 1 各循環器疾患の分布

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

表 2 データ欠損なし群とあり群の差

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

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

表 3 各職業における冠動脈疾患，脳卒中，循環器疾患全体のオッズ比

Characteristics		Control, %[a]	Case, %[a]	オッズ比 (95%信頼区間)[b]	
				モデル 1	モデル 2
冠動脈疾患, n		226,378	27,452		
職業					
ブルーカラー産業	ブルーカラー職	34.6	33.6	1.00	1.00
	サービス職	13.9	13.8	1.09 (1.04–1.13)	1.08 (1.04–1.13)
	専門職	4.1	3.8	1.05 (0.97–1.13)	1.07 (0.99–1.16)
	管理職	4.5	4.9	1.19 (1.11–1.27)	1.19 (1.11–1.27)
サービス産業	ブルーカラー職	4.1	3.9	1.01 (0.94–1.09)	1.01 (0.93–1.08)
	サービス職	15.8	16.8	1.10 (1.06–1.15)	1.10 (1.06–1.15)
	専門職	0.9	0.9	1.13 (0.97–1.32)	1.16 (0.99–1.35)
	管理職	2.2	2.4	1.20 (1.09–1.31)	1.19 (1.08–1.31)
ホワイトカラー産業	ブルーカラー職	2.1	2.1	1.07 (0.98–1.18)	1.08 (0.99–1.19)
	サービス職	9.4	9.2	1.04 (0.99–1.09)	1.05 (1.00–1.11)
	専門職	7.0	7.0	1.05 (0.99–1.11)	1.10 (1.04–1.17)
	管理職	1.5	1.5	1.06 (0.94–1.19)	1.06 (0.95–1.19)
喫煙[c]		2.1	2.3		1.15 (1.14–1.16)
飲酒[c]		2.3	2.2		0.95 (0.94–0.96)
狭心症, n		163,736	19,781		
職業					
ブルーカラー産業	ブルーカラー職	34.1	32.8	1.00	1.00
	サービス職	13.9	14.1	1.12 (1.06–1.18)	1.11 (1.05–1.17)
	専門職	4.1	4.0	1.10 (1.00–1.21)	1.11 (1.02–1.22)
	管理職	4.4	4.9	1.24 (1.14–1.34)	1.23 (1.14–1.33)
サービス産業	ブルーカラー職	4.1	3.7	0.92 (0.84–1.01)	0.92 (0.84–1.01)
	サービス職	16.2	16.9	1.08 (1.03–1.14)	1.08 (1.03–1.13)
	専門職	0.9	0.9	1.13 (0.90–1.42)	1.15 (0.92–1.45)
	管理職	2.2	2.4	1.21 (1.08–1.35)	1.19 (1.07–1.34)
ホワイトカラー産業	ブルーカラー職	2.1	2.1	1.11 (0.99–1.24)	1.12 (1.00–1.25)
	サービス職	9.4	9.3	1.05 (0.99–1.11)	1.06 (1.00–1.12)
	専門職	7.1	7.4	1.08 (1.01–1.15)	1.12 (1.05–1.19)
	管理職	1.5	1.5	1.12 (0.98–1.28)	1.12 (0.98–1.28)
喫煙[c]		2.0	2.2		1.11 (1.10–1.12)
飲酒[c]		2.2	2.2		0.98 (0.97–0.99)
急性心筋梗塞		62,642	7,671		
職業					
ブルーカラー産業	ブルーカラー職	35.8	35.6	1.00	1.00
	サービス職	13.9	13.0	1.01 (0.93–1.11)	1.01 (0.92–1.10)
	専門職	4.1	3.5	0.92 (0.80–1.06)	0.97 (0.85–1.12)
	管理職	4.7	4.8	1.07 (0.95–1.21)	1.07 (0.95–1.22)
サービス産業	ブルーカラー職	3.9	4.7	1.25 (1.09–1.42)	1.25 (1.09–1.43)
	サービス職	14.6	16.3	1.16 (1.07–1.26)	1.16 (1.07–1.26)
	専門職	0.9	0.9	1.12 (0.82–1.52)	1.17 (0.86–1.59)
	管理職	2.2	2.5	1.18 (1.00–1.38)	1.18 (1.00–1.39)
ホワイトカラー産業	ブルーカラー職	2.3	2.2	0.98 (0.78–1.24)	1.00 (0.78–1.28)
	サービス職	9.4	8.9	1.01 (0.91–1.11)	1.03 (0.93–1.14)
	専門職	6.6	6.2	0.98 (0.85–1.12)	1.06 (0.92–1.23)
	管理職	1.5	1.3	0.90 (0.67–1.21)	0.92 (0.68–1.24)
喫煙[c]		2.2	2.6		1.25 (1.22–1.27)
飲酒[c]		2.4	2.1		0.88 (0.86–0.89)
脳卒中, n		*n* = 312,675	*n* = 41,038		
職業					
ブルーカラー産業	ブルーカラー職	40.1	43.0	1.00	1.00
	サービス職	12.1	11.3	0.94 (0.90–0.98)	0.93 (0.89–0.97)
	専門職	3.2	2.4	0.77 (0.70–0.85)	0.77 (0.70–0.85)
	管理職	4.0	3.6	0.91 (0.85–0.97)	0.88 (0.83–0.95)
サービス産業	ブルーカラー職	4.0	4.5	1.08 (1.02–1.15)	1.08 (1.02–1.15)

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

[a] 多重補完から推定

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

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

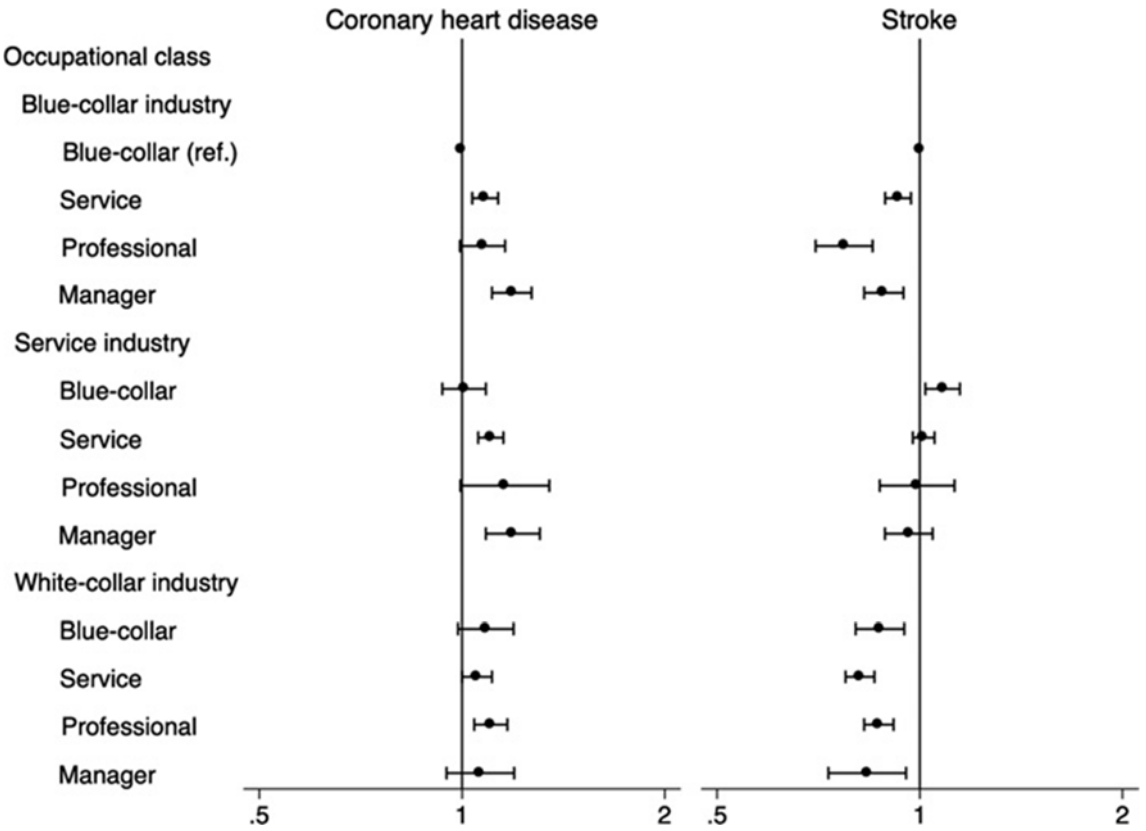

図 1 各職業と関連する冠動脈疾患と脳卒中のリスク。 オッズ比(点)と 95%信頼区間(線)は多重補完法を用いた年齢，病院，入院施設，入院年をマッチさせた条件付きロジスティック回帰分析により，喫煙と飲酒を追加調整して求めた(*Zaitsu M, et al. Occupational Class and Risk of Cardiovascular Disease Incidence in Japan: Nationwide, Multicenter, Hospital-Based Case-Control Study. J Am Heart Assoc. 2019;8(6):e011350*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

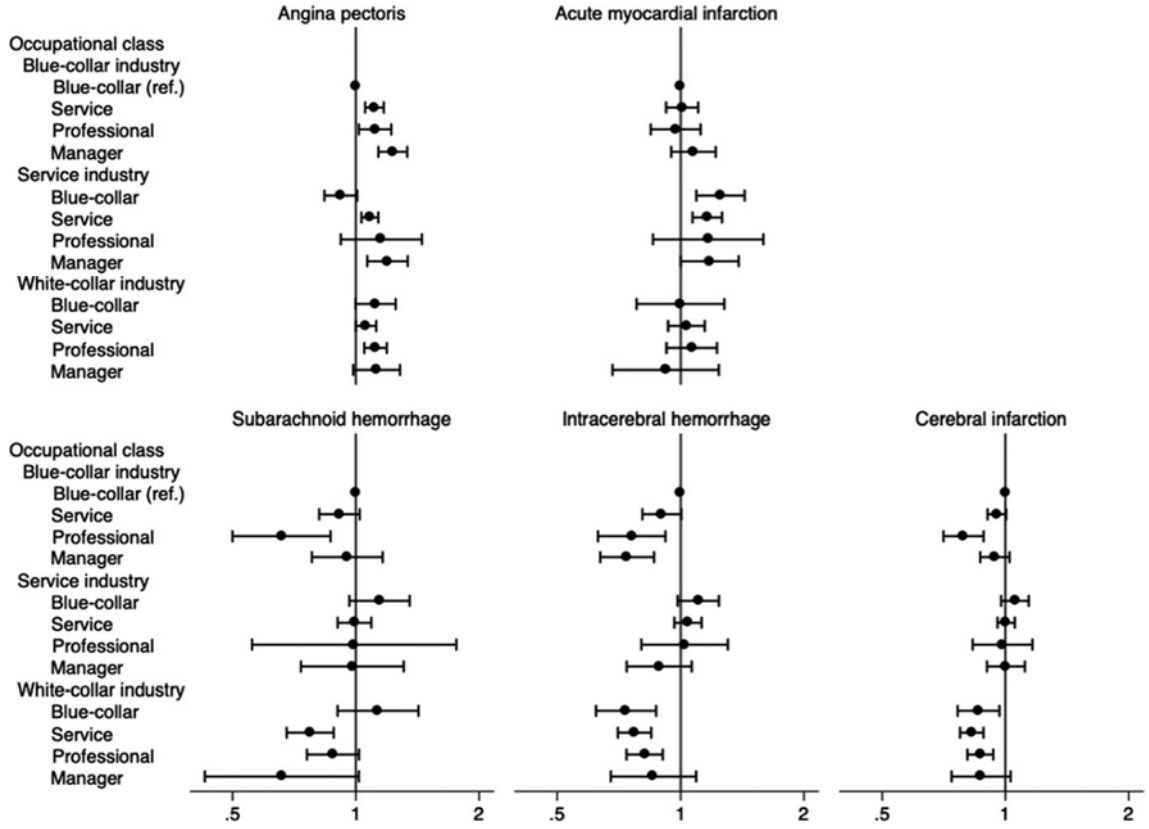

図 2 各職業と関連する狭心症，急性心筋梗塞，くも膜下出血，脳内出血，脳梗塞のリスク。 オッズ比（点）と 95%信頼区間（線）は多重補完法を用いた年齢，病院，入院施設，入院年をマッチさせた条件付きロジスティック回帰分析により，喫煙と飲酒を追加調整して求めた（*Zaitsu M, et al. Occupational Class and Risk of Cardiovascular Disease Incidence in Japan: Nationwide, Multicenter, Hospital-Based Case-Control Study. J Am Heart Assoc. 2019;8(6):e011350*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

資料 1　職業・産業による種々のがんの標準化罹患比（standardised incidence ratios）

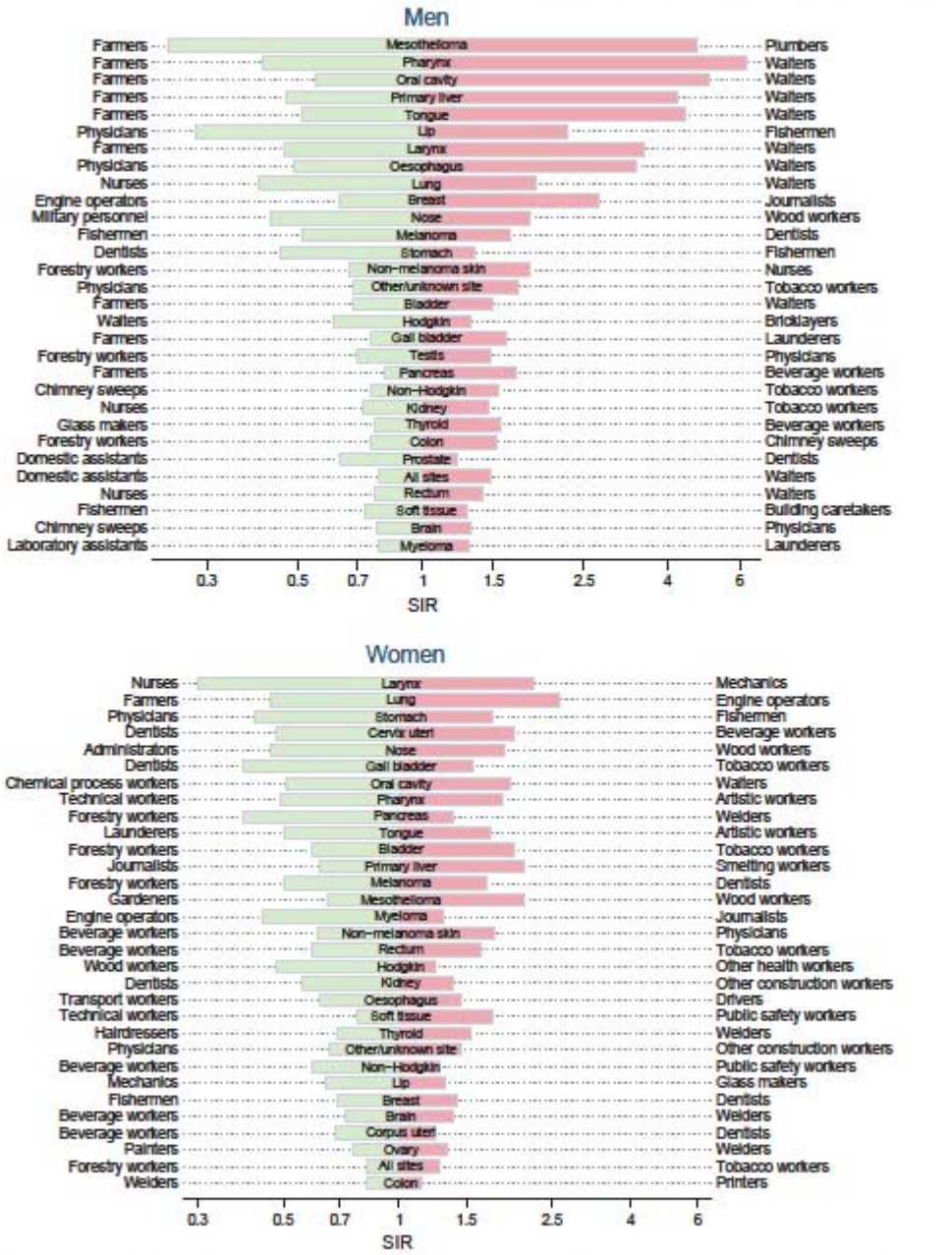

Figure 51. Risk of cancer in occupations with the highest and lowest standardised incidence ratios (SIR), by gender. Only occupations with ≥1000 workers, ≥5 observed cases and ≥5 expected cases have been included.

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

II. 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

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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、膀胱腫瘍組織における ZNF668 蛋白発現、ZNF668 遺伝子構造を検討した。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、2例の G-CSF 産生尿路上皮癌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。それらのゲノムを基に ZNF668、G-CSF、TLR2TIR、TLR4TIR、MyD88 遺伝子の塩基配列および G-CSF 遺伝子コピー数を検討した。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、筋層浸潤と関連していた。膀胱腫瘍ゲノムにおける ZNF668 遺伝子変異の頻度は低かった。G-CSF 産生腎盂癌症例では G-CSF 遺伝子の promoter 領域に -434G>C、intron 2 に c.204+345C>T、stop codon の下流に c.624+955C>G の heterozygous な体細胞変異を検出した。G-CSF 産生膀胱癌症例の成因は G-CSF、TLR2TIR、TLR4TIR、MyD88 遺伝子の変異および G-CSF 遺伝子コピー数異常によるものではなかった。

(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。G-CSF 産生尿路上皮癌における G-CSF 蛋白過剰産生の成因は、G-CSF 遺伝子の non-coding 領域の体細胞変異によることも考えられる。

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、あるいは

suppressor の破壊により膀胱腫瘍が生じうる。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。

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 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。

ZNF668 mRNA には 4 種類の variant があり、variant 1,2,4 は ZNF668 isoform α、variant 3 は ZNF668 isoform β を生成する。Variant 2 は3つの Exon より構成され、Exon2,3 に ZNF668 蛋白に翻訳される coding 領域が存在する。

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、この G-CSF 産生腫瘍由来ゲノムについて解析した。

この場合の白血球増多症における顆粒球形成(granulopoiesis)の成因の可能性としては、膀胱における Toll-like receptor (TLR)の関与も考えうる。TLR を介するのシグナルの刺激によって G-CSF が産生されうる。今回、膀胱腫瘍組織での TLR2, 4 の細胞内 domain(TIR)の変異、および TIR と結合する MyD88 の変異を検討した。

B. 研究方法

膀胱腫瘍ゲノムにおける ZNF668 遺伝子解析

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 mRNA variant2 を構成する 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直接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。

膀胱腫瘍組織における ZNF668 蛋白発現解析

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。

腫瘍組織における G-CSF 蛋白発現の解析

G-CSF 産生尿路上皮癌組織とコントロールの G-CSF 非産生膀胱癌組織に対し、抗 G-CSF 抗体(Santa Cruz Biotechnology, sc-53292)、を用いた組織免疫染色を施行した。

G-CSF 遺伝子の解析

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直接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。更に PCR1 は Seq1 および Seq2、PCR2 は Seq3、PCR3 は Seq4 プライマーでシークエンシングを追加した。

また上記の症例の尿路上皮癌組織ゲノムに対し、G-CSF 遺伝子、AP3B1 遺伝子(コントロール)の陽性 droplet 数をデジタル PCR 法で測定し、あるゲノムにおける AP3B1 遺伝子のコピー数を 2 と仮定して G-CSF 遺伝子のコピー数を算出した。

TLR2TIR、TLR4TIR、MyD88 遺伝子の解析

G-CSF 産生腫瘍症例とコントロールの G-CSF 非産生腫瘍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 TLR2TIR、TLR4TIR、および MyD88 遺伝子を PCR 法にて増幅し、更にそれらの増幅産物を直接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 3 に示す。

(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

1.　膀胱腫瘍における ZNF668 の解析

膀胱腫瘍組織における ZNF668 蛋白発現解析

48 例の膀胱腫瘍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 4 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。

膀胱腫瘍ゲノムにおける ZNF668 遺伝子解析

表 5 に示すように、ZNF668 遺伝子の Exon1 の解析では 58 検体中 3 検体(5.2%)に SNP データベースに見られない 2 種類の heterozygous な遺伝子変異を検出した。また一塩基多型(SNP)rs2303222 を検出した。Exon2 の解析では 64 検体中 6 検体(9.4%)に SNP データベースに見られない同一の heterozygous な変異を検出した。Exon3 の解析では 42 検体中 4 検体(9.5%)に SNP データベースに見られない 5 種類の heterozygous な遺伝子変異を検出した。Coding region に見られた Exon2 の 1 変異と Exon3 の 1 変異は silent であったが、Exon3 の他の 2 変異はアミノ酸の置換をもたらすものであった。Exon1 の 2 変異と Exon3 の 2 変異は各々5'-UTR、3'-UTR に存在した。

また上述のように検出した変異と ZNF668 蛋白の膀胱腫瘍組織における発現の強弱との関連は、見出せなかった。

2.　尿路上皮腫瘍における G-CSF の解析

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
G-CSF 産生膀胱癌症例、G-CSF 非産生膀胱癌症例では、血液、腫瘍ゲノム間で G-CSF 遺伝子の塩基配列の違いは認めなかった。しかし G-CSF 産生腎盂癌症例において、promoter 領域に-434G>C、intron 2 に c.204+345C>T、stop codon の下流に c.624+955C>G の heterozygous な体細胞変異と思われる変異を検出した(図 2)。これらの変異は SNP データベースには登録されていなかった。

G-CSF 遺伝子コピー数の解析
表 6 に示すように、G-CSF 産生尿路上皮癌組織ゲノムにおいて、明らかな G-CSF 遺伝子 copy 数の増加は認めなかった。

TLR2TIR、TLR4TIR、MyD88 遺伝子の解析
G-CSF 産生、非産生膀胱腫瘍、および対応する血液ゲノムにおいて、参照の塩基配列と比べて変異は検出しなかった。

D. 考察
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。しかしながら ZNF668 遺伝子の coding 領域に見られる変異の頻度は比較的少なく、ZNF668 蛋白の膀胱腫瘍組織における発現を調節するものとは言えない。従って膀胱腫瘍における ZNF668 蛋白発現は ZNF668 以外の因子による二次的な制御、あるいはメチル化等による ZNF668 遺伝子における epigenetic な要因によるのかもしれない。

G-CSF 産生腎盂癌症例の non-coding 領域に SNP ではない3種類の変異が認められた。この中に癌細胞における G-CSF の過剰産生を引き起こす変異が存在することも考えられる。特に-434G>C は promoter 領域における変異であり、その可能性が高いのかもしれない。このことについては更なる検証の必要性がある。

G-CSF 産生膀胱癌症例における G-CSF 産生の成因については今回の検討では解明できなかった。G-CSF 産生膀胱癌症例における G-CSF、TLR2TIR、TLR4TIR、MyD88 遺伝子の塩基配列については血液 G-CSF 遺伝子、参照配列との差異はなく、G-CSF 産生の要因ではない。また G-CSF 産生膀胱癌症例における G-CSF 遺伝子コピー数の増加も認めず、これも G-CSF 産生との関連は考えられない。

E. 結論
① 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が、膀胱癌組織における ZNF668 遺伝子変異の頻度は低かった。

② G-CSF 産生腎盂癌症例における G-CSF 過剰産生は、G-CSF 遺伝子の non-coding 領域の体細胞変異が成因である可能性がある。

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

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奥野佑美子、田中 亮、三上 耕治、武内 巧 転移性腎細胞癌に対する nivolumab / ipilimumab 併用療法後の腎癌組織の検討 泌尿器科紀要 66: 13-17, 2020.

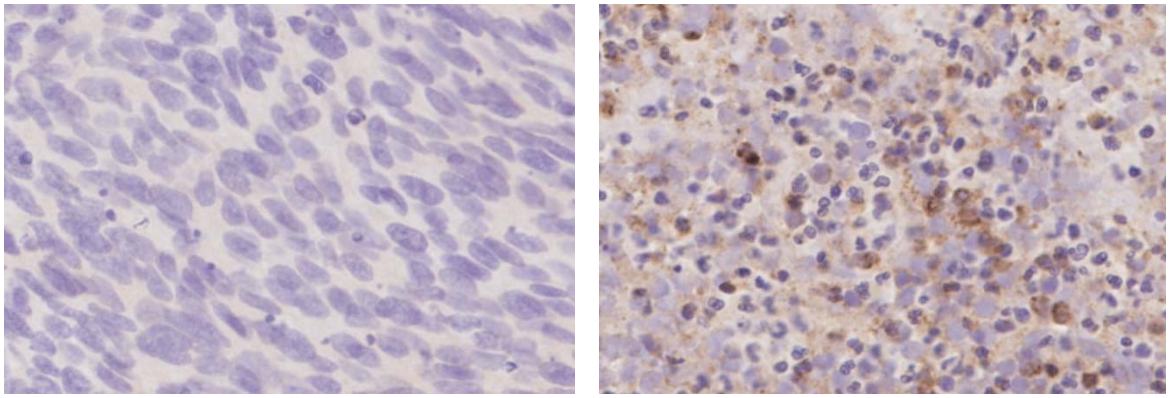
2. 学会発表

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

図 2:GCSF 産生腎盂癌にみられる non-coding 領域の heterozygous な変異

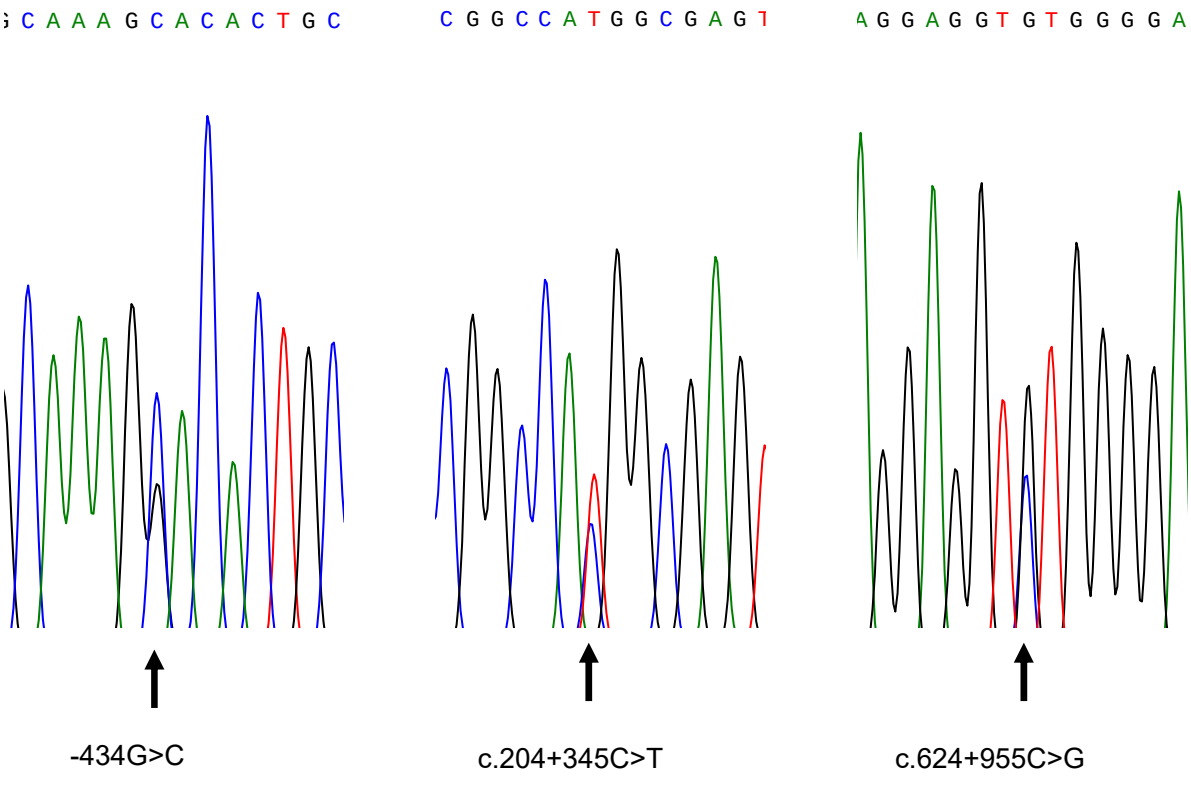


表1：ZNF668 遺伝子の増幅に用いたプライマー

ZNF668_Ex1 (sense):	5’–gtccttaggtgcaaaagcttccccg–3’
ZNF668_Ex1 (antisense):	5’–ccgcagggaaactgaggccagctc–3’
ZNF668_Ex2 (sense):	5’–tgaggctttcaggagtggcgaaggt–3’
ZNF668_Ex2 (antisense):	5’–ttaccctgagactcaaacccaggcc–3’
ZNF668_Ex3 (sense):	5’–gcagtggggtcacgttatgggtctg–3’
ZNF668_Ex3 (antisense):	5’–tgatgcccaaactcccacccattca–3’

表 2：G-SCF 遺伝子の増幅・シークエンス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’
Seq1:	5’– atcacgaggtcaggagatcgtgac –3’
Seq2	5’– aactctccggaggctgcctgtctg –3’
Seq3:	5’– gcttcctgctcaagtgcttagagc –3’
Seq4:	5’– gtcacattgtaactgaacttcagg –3’

表 3：TLR2_TIR、TLR4_TIR、MyD88 遺伝子の増幅に用いたプライマー

TLR4_TIR (sense):	5’– acctgatgcttcttgctggctgcataaag –3’
TLR4_TIR (antisense):	5’–tcagatagatgttgcttcctgccaattgca –3’
TLR2_TIR (sense):	5’–ccgtttccatggcctgtggtatatgaa –3’
TLR2_TIR (antisense):	5’–ctaggactttatcgcagctctcagat –3’
MyD88 (sense):	5’–gggatatgctgaactaagttgccac –3’
MyD88 (antisense):	5’–gacgtgtctgtgaagttggcatctc –3’

表 4: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

表 5:膀胱癌組織における ZNF668 遺伝子変異とアミノ酸変異

Exon 1	Exon 2	Exon 3
c.-567G>A (5'-UTR)	c.606C>T (silent)	c.695G>T (p.S232I)
c.-76C>T (5'-UTR)		c.984T>C (silent)
		c.1603G>C (p.E535Q)
		c.1895C>T (3'-UTR)
		c.2028C>G (3'-UTR)

表 6:尿路上皮癌組織における GCSF 遺伝子コピー数

腫瘍分類	G-CSF 遺伝子の copy 数
G-CSF 産生膀胱癌	2.12
G-CSF 産生腎盂癌	1.46
G-CSF 非産生膀胱癌	3.25
G-CSF 非産生膀胱癌	1.97
G-CSF 非産生膀胱癌	1.21

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及び神奈川県悪性新生物登録事業地域がん登録を用いた癌と職業に関する疫学的サーベイランス

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研究要旨

職業疾病は、人が従事する産業を取り巻く社会環境、作業に付随するリスク要因への曝露、産業から生まれる socioeconomic status 等、あらゆる要因から形成される。

その要因を特定するためには、近年利活用の場が広まっているビッグデータを利用し、職業・産業がどのように疾病の発生・予後に差を与えているか評価することが必要である。

（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、事業場における有害物質曝露の機会が多いとされる製造業について、各製造業の各種癌(前立腺癌、尿管癌、腎臓癌、膀胱癌、食道癌、肝臓癌、膵臓癌、大腸癌、肺癌、乳癌）に対するオッズ比を算出した。既知の癌リスクである飲酒、喫煙などの因子を調整した後、木材・木製品業でオッズ比が 0.51-0.83 と他の職種より低値を示した。なめし革・同製品・毛皮製造業で、肝臓癌 2.36(95%CI 1.15-4.38), 膵臓癌で 2.85(95%CI 1.26-6.47)、肺癌で 2.00（95％CI 1.01-3.99）、電気機械器具製造業で尿管癌 2.09(95%CI 1.18-3.70)、腎臓癌 2.49(95%CI 1.79-3.55)と尿路系の癌リスクが高値となった。オッズ比が 2.0 以上となった癌腫と産業の組み合わせに含まれる症例につき、入院病歴に遡って癌の組織学的確定診断を得られたものは 89%に上った。

（2）神奈川県悪性新生物登録事業を用いて、登録施設規模の観点から登録症例の傾向及び予後の差について検討した。症例登録数によって施設規模を分類すると、全癌種に於いて、大規模施設で診断時年齢は低く、予後が長い傾向を認めた。Propensity score matching を用いて症例の背景を揃えても、結果は同様であった。を診断時病期に関し、胃癌と肺癌では、大規模施設で Stage I の割合が高く、Stage IV の割合が低かったが、他の癌では偏りを認めなかった。

（3）非識別加工情報として提供された神奈川県悪性新生物登録事業のがん登録情報と、ICOD-R に登録された症例を突合し、相互に欠損する情報を補完したデータを作成した。突合データから各産業ごとの癌の5年生存率を算出した。突合し得たのは 13,234 件であり、そのうち代表的な固形癌で職歴の登録があるものは 4,630 例であった。Kaplan-Mayer 曲線により 5 年生存率を算出すると、一

次産業従事者は、二次、三次産業従事者に比べて有意に生存率が低かった（43.1%、 54.5%、57.0%）。

本研究で、従事する職業・産業が発癌リスク、診断確定後の予後と関連する可能性が示唆された。また、異なる状況下で集積されたデータの突合により、希少な新規知見を得ることが期待される。

A. 研究目的

人が日常生活の中で長時間従事する「仕事」は健康に多大な影響を与える。癌も同様であり、それは職業による発がんリスク物質への曝露はもとより、作業環境、就労形態や職業によって規定される socioeconomic status (SES)等が影響することもある。

職業に起因した疾病の発生には、長い時間がかかることも多く、個々が別の医療機関に受診していることが多いため、職業集積性を捉えられることは珍しい。また、職業や就労状況に対する医療機関側の注目の欠如は、集積性を捉える機会を更に減少させている。

このような現状を踏まえ、ビッグデータを用いて職業・産業ごとの疾病動態の特性を把握することは、新たな職業関連疾病に気づきを起こすきっかけとなる。

本研究では、ビッグデータを用いて職業・産業の疾病リスクと予後への影響について、職業集積性を推定することで、職業上曝露などの職業関連リスクの可能性を推定することとした。

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（ICOD-R）及び、人口 900 万を超える日本第二の都市である神奈川県で集積された、日本最大級の地域がん登録である。

① 各種製造業従事者による癌リスクの検討

職業上の発がん物質曝露による癌の罹患は未だに不明な点も多く、あらゆる規制がされていても新たな関連の報告は絶えない。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）。この情報をもっても、特殊な状況下の有害化学物質の高濃度曝露は予測不可能であるが、産業ごとに曝露されやすい物質の推定には利用できる。

そこで、ICOD-R を用い、各製造業の癌リスクの検討を行い、PRTR を参考に、産業に起因した化学物質曝露との関連について考察した。

② 医療機関の症例登録数で層別化した受診者の傾向と疾病予後の分析

国民皆保険制度のもと、日本国内の医療水準には強い不均一性は無いと考える。しかし、医療機関ごとに社会の医療の担い手としての使命は異なり、受診者特性も異なる。また、疾病の診断時期は、受診者個人の特性や、居住地

区周辺地域の SES に左右される可能性もある。加えて、医療機関の得意不得意や設備規模は予後に影響するであろう。そこで、登録施設規模の別で受診者や治療アウトカムの代表的指標となる予後にどのような傾向があるかを検討した。

③ 神奈川県地域がん登録と ICOD-R の突合に
よる産業と疾病予後の関連性の検討

ICOD-R は過去 4 件の職歴登録や生活習慣病登録を有した入院情報であるが、入院対象となった疾病に関して、当該入院以後の転機、予後、死亡記録が無い。一方で地域がん登録は診断確定からの予後を追跡できるものの、職歴登録は国勢調査時の統計に限られる。更に死亡個票からの職歴採歴は、死後の死亡届届出者による記載であるため、正確性に乏しい。そこで、両者を突合することで、職業・産業ごとの各疾病の予後の差を捉えることを目的とする。

B. 研究方法

① 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（前立腺、乳房、腎、尿管、膀胱、食道、胃、肝臓、膵臓、大腸、肺）のリスクについて、最も症例数の多い食品製造業を reference とし、喫煙量・飲酒量を調整した上で、ロジスティック回帰分析を用いて各製造業の癌のオッズ比を算出した。

ICOD-R の特徴として、匿名化のまま入院病歴要約に遡ることが可能であるため、オッズ比 2.0 を超えた製造業と癌の組み合わせについて、全国労災病院から該当病歴要約を取り寄せ、組織学的な癌の確定診断が存在することを確認し、結果の信頼性を高めることとした。

② 医療機関の症例登録数で層別化した受診
者の傾向と疾病予後の分析

神奈川県悪性新生物登録事業より得たデータから、各種癌の病期分類（TNM stage）別 5 年生存率を算出した。次に、各種癌の登録症例数で登録施設（医療機関）を分類し（以下「登録施設規模」と記載）、癌種、登録施設規模ごとに 5 年生存率を算出した。また、全体の 25%を占める登録症例上位の施設とそれ以外の施設で、年齢、性別、登録年代、診断病期を Propensity score matching を用い調整した上で施設規模による生存率の差を検討した。を更に登録施設規模による登録症例の特性および診断時病期分類（TNM stage）の割合を解析した。

③ 神奈川県地域がん登録と ICOD-R の突合に
よる産業と疾病予後の関連性の検討

ICOD-R と神奈川県地域癌登録はいずれも非識別加工情報として提供される。そこで、年齢、性別、居住地区、疾患名、届出医療機関の情報を用いて情報を突合した。突合可能であった症例より、各癌の産業別 5 年生存率を算出した。

解析には STATA/MP15.0 software (Stata-Corp LP, College Station, TX)を用いた。

ベースライン特性は $\chi 2$ 乗検定を用いて解析した。リスクに関連する要因のオッズ比は Cox 比例ハザードモデルを用いて算出した。*P*

値は 両側検定で、< 0.05*、< 0.01** 及び < 0.001***を統計学的有意とした。
5 年生存率は Kaplan-Meier 曲線を用い、ログランク検定を行った。

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易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癌を対象とした疫学的研究」の承認を得て実施した。

C. 研究結果

①各種製造業従事者による癌リスクの検討

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くため初回入院に限ると 418 万件、そのうち職業の登録のあるものは 183 万件であった。

そのうち前立腺、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、製造業は 40,370 例であった。

表1に製造業におけるベースライン特性の分布を示す。乳がんの平均入院時年齢は、最も低く 55.1±12.1 歳、他の癌腫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は低い傾向であった（50.7 ± 11.3, 56.8 ± 10.7, 56.6 ± 11.6, 58.6 ± 11.9 歳）。

各製造業ごとの喫煙量、飲酒量の分布を表 2 に示す。いずれの製造業でも、喫煙量飲酒量ともにコントロールに比して 75 パーセンタイル値は高いが、中央値に特筆すべき差は認めなかった。

表 3 に、40,370 例を用いたロジスティック分析で得た各産業のオッズ比を示す。

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、ゴム製品製造業の尿管癌 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) 、膵臓癌で 2.85 (95% CI 1.26–6.47)であった。

電気機械器具製造業では腎臓癌で 2.49 (95% CI 1.75–3.55), 尿管癌で 2.09 (1.18–3.70)であった。情報通信機械器具製造業では腎臓癌が 2.69 (95% CI 1.77–4.11), 尿管癌が 2.14 (95% CI 1.02–4.45)であった。

オッズ比 2.0 以上と算定された項目について、その根拠となった症例の病歴要約から、組織学的所見を得た結果を示す。

オッズ比が全癌で高い傾向となったなめし革・同製品・毛皮製造業の全ての症例は 106 例であり、そのうち 44 例の病歴要約を入手し

得たが、残 62 例は破棄済みであった。更にその中で 30 例の病理学的癌の診断を得た。その他オッズ比が 2.0 を超えた産業と癌の組み合わせについては以下の通りである。

電気機械、電気通信、電気部品の腎臓癌で 134 例のうち、77 例の病歴が入手可能であり、57 例が破棄された。77 例中 76 例で病理学的癌の診断が確認可能であった。印刷業、ゴム製造業、電気機械器具製造業、情報通信機械器具製造業の尿管癌 61 例のうち、34 例の病歴要約が入手可能であり、27 例は破棄された。34 例中 33 例で病理学的に癌の診断を確認した。以上より、なめし革・同製品・毛皮製造業及びオッズ比 2.0 以上を示した癌と産業の組み合わせに当たる症例で、入手可能であった病歴要約のうち、病理組織学的に癌の診断を確認できたものは 89.7%に上った。

②医療機関の症例登録数で層別化した受診者の傾向と疾病予後の分析

神奈川県地域癌登録から取得したデータより主要癌の TNM stage 別の 5 年生存率を Kaplan-Mayer 曲線で示した（図 1）。いずれの癌も stage1 2 3 4 の順で予後が良好であり、データの精度と妥当性裏付けられた。

登録施設規模ごとの登録症例のベースライン特性を表 4 に示す。いずれの癌でも、登録施設規模が大きいほど診断時年齢が低い傾向となった。

診断時病期との関連では、胃癌で 1000 例以下の施設で stage1 が 51.25%に対し 3000 例以上の施設で 62.39%、stage4 が 26.96%に対し 17.82%、肺癌では 1000 例以下の施設で stage1 が 26.41%を占めたのに対し 3000 例以上の施設で 42.85%, stage4 が 47.12%に対し 29.17%、

と大規模施設で早期症例の占める割合が多く、小規模施設で進行症例の割合が高い傾向があった。しかし、他の癌では登録施設規模と診断時病期の分布に明らかな不均衡は認められなかった。

図 2 に登録施設規模ごとの各癌の5年生存率を Kaplan-Mayer 曲線で示した。いずれの癌でも登録施設規模が大きいほど生存率が良い傾向を呈した。

表 5 に、登録症例全体の上位 25%を占める施設を High volume 施設とし、それ以外の施設とに分類した、症例の分布を示す。いずれの癌腫においても性別、年齢、診断時期、診断病期で差を認める。これらの症例を用いて Propensity score matching を行なった後の症例分布を表 6 に示した。マッチング後の症例で各癌の 5 年生存率を示したものが図3であり、すべての癌で High volume 施設の方がその他の施設より予後の延長が見られた。

③神奈川県地域がん登録と ICOD-R の突合による産業と疾病予後の関連性の検討

ICOD-R は全国のデータである一方、神奈川県地域癌登録は神奈川県に限られた全数調査である。従って、突合は主に ICOD-R のうち、神奈川県に立地する関東労災病院と横浜労災病院の登録症例と、神奈川県地域癌登録の「届出医療機関」と「死亡医療機関」のいずれかが関東労災病院と横浜労災病院であるものに限られた。突合作業の経過を図 4 に示す。ICOD-R のうち関東労災、横浜労災で登

録された癌の症例は 29,803 件、神奈川県地域癌登録より関東労災、横浜労災が届出医療機関もしくは死亡医療機関となった症例は 27,698 件であり、突合可能であったのは 13,234 件となった。そのうち前立腺、乳腺、腎臓、膀胱、食道、胃、肝臓、膵臓、大腸、乳腺、肺の癌腫に該当する症例は 8,795 件であり、更に職歴登録があるものは 4,630 例、そのうち TNM 病期分類があるものに限ると 3,527 例となった。

突合後全症例のベースライン特性を表 7 に示す。食道癌と肺癌で Brinkman 係数と飲酒量が多い傾向が見られた。

これらの各癌の 5 年生存率を Kaplan-Mayer 曲線で描いたものが図 5 である。それぞれの 5 年生存率は前立腺癌 72.2%,腎臓癌 76.4%, 膀胱癌 71.0%,食道癌 28.6%,胃癌 51.0%、肝臓癌 23.6%,膵臓癌 7.5%、大腸癌 57.2%、乳癌 85.0%、肺癌 27.9%であった。

更に、職業登録がある 4,630 例に限り、産業別の症例のベースライン特性を表 8 に示した。職業登録のあるものに限ると突合症例全体の半数に減少したが、ベースライン特性は突合例全体と同様で、食道癌と肺癌で Brinkman 係数と飲酒量が高い傾向を示した。また産業別では第 3 次産業で喫煙・飲酒量が著しく低かった。

癌腫ごとの 5 年生存率を図 6 に示す。また産業別の 5 年生存率を図 7 に示す。産業ごとの 5 年生存率は1次産業で 43.1%であり、2 次産業 53.5%、3 次産業 54.7%に比して有意に低かった。図 8 は癌腫ごとに産業別の生存率を示したものである。膀胱癌(一次 0%、二次 76.2%、三次 77.3%)と胃癌(一次 40.0%、二次 60.7%、三次 56.9%)では一次産業で有意に生存率が低かった。

職歴登録と診断時病期分類が揃った症例について、産業ごとの診断病期の分布を表 9 に示す。食道癌と乳癌は、三次産業の Stage 1 の占める割合が二次産業に比して高かった (52.6%、47.7%)。一次産業で病期登録があるものは極めて少なく、分布の偏りは評価できなかった。

D. 考察

① 各種製造業従事者による癌発症リスクの検討

本研究で使用した ICOD-R は、患者自らが記載した正確な職歴登録や生活習慣病歴などの情報を有するものの、それらは強制的な登録ではなく、患者の自発的な登録辞退が可能であることからデータの欠損値が多いことが問題点である。しかし、個人情報保護の観点からは、強制的に聴取することもできず、日々蓄積されていくデータの精度をどのように上げていくかが大きな課題である。

よって、職歴登録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就労人口の少ない職業のオッズ比が統計モデル上収束しないため、入院時期、登録施設(病院)、飲酒量、喫煙量のみを共変量としたモデルとした。もっとも、ICOD-R の特徴を最大限に捉え、結果の信頼性を出来る限り高めるため、オッズ比の高い製造業と癌との組み合わせに該当する症例について、病理組織学的根拠を可能な限り追跡することを試みた。

木材・木製品製造業では、前立腺、膀胱、食道、胃、肝臓、膵臓、大腸のいずれにおいてもリスクが低い結果となった。この業種に限ったリスク低下、増加の報告は見受けられなく、また、同製造業の喫煙飲酒量は他製造業と際立った差異は認めなかった。職業性曝露の観点から Pollutant Release and Transfer Register(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。

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、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、途上国では労働環境の劣悪な状況での低年齢層の労働が問題視されている他、なめし作業過程の職業性曝露は高い発がんリスクと関連するとの報告が多数ある。一方で本邦では、職業選択の余地が幅広く、熟練した職人として好んで同職業に就く機会が多く、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であろう。優れた革製品を生産するイタリアからの報告では、本研究結果と同じくなめし革・同製品・毛皮製造業の胃癌と膵臓癌と肺癌のリスク増加が報告されている。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/年と製造業の中で最も高く、中小の工房で行われるような業態での作業環境管理が行き届かず、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まだ見受けられないが、電力及び情報通信業の発展は著しく、半導体製造所での有害作業業務と発がんリスクの報告が中国などから増加している。同分野の作業行程は非常に幅が広いが、多くの科学物質、光、溶媒、酸、気体を扱うため、今後新しい作業関連発癌が報告されてくる可能性も高い。本研究もその前兆の一端と言えるであろう。

本研究では、ICOD-R の最大の特徴の一つである、「匿名化のまま入院病歴に遡ることができる」特徴を利用し、近年臨床上は必須となった癌の確定診断のための病理組織学的証拠にまで遡るアプローチを行った。カルテ保存期間を超過したことによる破棄の他、膵癌の様に、以前は病理組織学的証拠を得ることが困難であった疾患、また CT や MRI、腫瘍マーカーにより実質上癌が確定しているが、その症例の背景や予後を鑑み、病理組織学的診断まで追求しない症例など、個々の臨床現場での問題から組織学的証拠が得られないケースも多い。そのような中、約 90%の病理組織学的診断まで遡ることが可能であったということは、ICOD-R の精度の高さと緻密さ故である。また、全国労災病院群で行われた医療の信頼性を担保する証拠と言える。

②医療機関の症例登録数で層別化した受診者の傾向と疾病予後の分析

登録施設規模が大きいほど予後が良い最大の要因は、症例が若い点であろう。若年者の方が医療アクセスの幅は大きく、また若年者の

方がより一般的に医療の質が高いという認識のある大病院を受診することが予測される。また、医療者側にも、患者の年齢による紹介先の割り振り等、施設規模によって患者構成の偏りが生じる動機が存在する。

一方で登録施設規模と診断時病期は胃癌と肺癌を除き、偏りが見られなかった。

肺癌について、大規模施設では間質性肺炎や慢性閉塞性肺疾患を長期フォローアップしていく中で癌を発症することも多く、早期に診断される可能性や、放射線科が独立した部門として存在することで発見契機が増加している可能性が挙げられる。しかし同様の傾向は長年の肝硬変のフォローアップの結果発生する肝臓癌では見られていない。胃癌は最終的に内視鏡で診断されるが、健診のスクリーニングはまだ胃透視に依存している部分も多く、要精査となった症例の紹介が大病院に集中している可能性が挙げられる。以上から考慮すると、胃癌と肺癌に特徴的な事業として、検診、スクリーニングが発達しており、検診事業の 2 次読影を担う大規模施設に早期病変が集中する可能性が考えられた。

ところで、甲状腺や乳腺に特化した病院があるように、症例登録数が多いことと、その施設規模が大きいことは必ずしも一致するものでは無いが、今回の集計では、各癌ともに最も登録施設規模の多い群に入った施設はいずれも大学病院などの大規模施設であった。これは神奈川県の病院事情を反映したものであるため、どの地域でも同様の傾向とは言えない。

③ 神奈川県地域がん登録と ICOD-R の突合による産業と疾病予後の関連性の検討

この作業は、非識別加工情報として提供されるビッグデータ同士の突合の可能性を模索する研究でもある。本来、労災病院群に入院した神奈川県地域住民である症例は全て突合されるはずだが、受け取っている両媒体は非識別加工されているため、突合症例数には限界がある。

突合するためには登録施設情報が必須であり、関東労災病院と横浜労災病院に限られた。1:1 で突合できたのは関東労災と横浜労災に関わる症例の約半数となった。

突合データ全体の傾向として、食道癌と肺癌で飲酒量、喫煙量が多い点は既知のとおりである。

また、一次、二次産業に比べ、三次産業で飲酒喫煙量が少ないことも既知の知見を踏襲するものであり、外的妥当性が認められた。

日本産業分類の中分類まで分類すると症例の少なさから予後の推定が困難であるため、一次産業、二次産業、三次産業に分類し、予後の分析を行った。農林業センサスによると、平成 27 年の農業・林業従事者は全体の 3.5%であるが、本研究では一次産業は 1.2%を占めるに過ぎなかった。これは横浜と川崎という大都市圏の症例に限定されたことが大きい。

本研究では、一次産業の癌の予後が、二次、三次産業に比して短い結果となった。昨年、我々は農業、林業など一次産業の癌リスクが他の職業に比して低い傾向にあることを報告したが、その際も、同業種の診断時年齢が高い点に着目した。今回の予後の結果も、最大の要因は就労者の年齢層とも考えらえる。

また、産業ごとの診断時病期も影響した可能性がある。本研究では一次産業の症例数が少なく、診断時病期の分布傾向は不明であった。しかし、二次、三次産業が企業に雇用されている就労形態が多く、産業医の管理指導によるヘルスチェック機能が強制的に働いている一方で、医療アクセスも遠く、家族経営も多い一次産業では、発見契機が遅れている可能性もある。

本研究において、ICOD-R が有さず地域がん登録が有するデータは主に死亡情報であり、地域がん登録が有さず ICOD-R に登録されている情報は全 4 種類の職業歴の他、喫煙量、飲酒量、生活習慣病歴（糖尿病、高血圧、高脂血症、高尿酸血症、肥満）が挙げられる。5 年ごとの国勢調査の年に、死亡小票には職業歴が登録される。しかし届出る際に家族が記入するものであり、死亡者が生涯の中で糧とした職業であるかは不明であり、思い出しバイアスも強い。一方で ICOD-R は全 4 職歴から、その最長を採用することで、当該患者が最も人生を費やしたであろう職業を同定して分析することができる。

ICOD-R は全国労災病院で 50 年近くにわたり各病院で蓄積されたデータであり、これまで表出される機会も少なかったが、地域癌登録と突合できたことで、ICOD-R の公的価値が立証できると考える。

(ア) でも述べたように、現在のところ、ICOD-R の職歴登録は強制ではないため、職歴の欠損値が大きなバイアスを生じさせてしまう。しかし、個人情報保護の観点からはこの課題を克服することは困難であり、詳細な職歴聴取を希望されない症例に関しては、少なくとも一次、二次、三次産業というような分類の登録を得ることが望ましい。

今後 ICOD-R は勤務のシフト制、雇用形態、喫煙形態など更に詳細な項目の収集が予定されている。全国癌登録をはじめとした、他のデータとの突合で更なる知見の飛躍が期待される。

E. 結論

本研究では、2種類のビッグデータの使用により、各種製造業での癌リスクが異なる可能性、医療施設規模によって症例の傾向や予後が異なる可能性、各種従事産業によって癌の予後が異なる可能性が示唆された。

データの欠測により、本結果を母集団に適応するには未だ難が多く存在するが、一層のデータ補完によってより強い因果を推定することが推奨される。

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

Kaneko R, Zaitsu M, Sato Y, Kobayashi Y. Risk of cancer and longest-held occupations in Japanese workers: A multicenter hospital-based case-control study. Cancer Med. 8(13),6139-6150: 2019

2.学会発表

なし

H. 知的財産権の出願・登録状況

なし

	All cancers	Prostate	Breast	Kidney	Ureter	Bladder	Esophagus	Stomach	Liver	Pancreas	Colon	Lung	Fracture(control)
All manufacturing categories n=	40,370	2,769	2,462	1,149	494	3,639	1,730	9,741	2,869	1,944	7,758	5,815	26,746
(male:female)	32,238:8,132	2769:0	49:2,413	978:171	430:64	3,376:263	1,612:118	7,989:1,752	2,518:351	1,535:409	5,991:1,767	4,991:824	20,006:6740
age(mean±SD)	65.3±11.4	68.8±9.0	55.5±12.1	62.5±11.5	69.4±9.9	68.5±11.2	66.4±9.6	64.1±11.7	64.2±10.5	66.4±10.6	65.6±11.1	67.5±10.5	50.8±17.9
Industrial category													
Food *n=3570* (male:female)	1,856:1,714	165:0	7:464	44:33	26:7	196:61	121:28	457:375	164:81	98:98	317:378	262:188	1,252:1,459
age(mean±SD)	63.6±11.5	69.6±8.56	56.3±11.1	61.1±11.9	68.9±10.5	68.2±11.7	65.3±8.9	62.7±11.4	63.5±10.6	65.3±9.9	64.9±11.1	64.9±11.2	53.5±18.3
Beverages, tobacco and feed *n=612* (male:female)	474:138	52:0	3:40	11:4	7:3	50:3	35:0	110:27	39:8	33:3	81:34	53:16	251:111
age(mean±SD)	65.9±10.8	70.8±9.4	55.7±12.5	63.8±12.8	69.3±6.4	67.6±11.6	68.1±6.4	63.8±11.2	66.7±8.2	67.3±9.8	65.9±10.0	68.6±9.8	52.9±18.2
Textile mill products *n=1022* (male:female)	729:293	62:0	1:74	27:5	15:2	80:11	40:7	175:65	71:16	38:19	106:69	114:25	267:210
age(mean±SD)	68.0±11.4	71.6±7.91	59.9±12.1	65.1±8.5	70.3±7.9	72.6±11.3	68.3±9.5	67.6±11.6	63.9±11.1	69.1±12.3	68.3±11.3	70.2±10.6	58.3±19.7
Clothes and other textiles *n=1721* (male:female)	595:1,126	50:0	0:340	20:19	6:15	67:28	27:13	160:228	50:55	37:50	116:247	64:129	248:878
age(mean±SD)	64.1±11.8	68.5±11.2	57.3±11.5	65.4±11.7	72.3±10.2	67.5±12.9	67±11.4	64.2±11.6	65.4±9.8	65.5±11.9	66.2±10.9	65.9±10.5	58.8±16.8
Lumber and wood products, except furniture *n=1319* (male:female)	1,129:190	94:0	2:49	35:5	16:4	112:8	57:2	299:39	74:8	55:10	186:46	199:19	761:190
age(mean±SD)	67.1±11.5	70.4±10.3	56.2±12.6	65.7±13.5	71.8±8.12	69.8±11.6	66.4±10.9	65.7±11.1	65.6±9.1	69.6±9.5	67.1±11.8	68.9±11.3	54.1±18.3
Furniture and fixtures *n=652* (male:female)	561:91	63:0	1:25	17:6	11:1	57:4	26:0	131:23	39:2	19:3	111:23	86:4	314:58
age(mean±SD)	66.2±11.1	70.7±9.7	57.7±11.4	60.4±8.3	74.5±7.82	68.8±9.5	66.7±8.5	64.7±12.5	64.4±12.5	67.2±10.7	65.6±10.5	68.4±10.0	53.5±187.5
Pulp, paper and paper products *n=1065* (male:female)	871:194	90:0	2:54	28:4	6:1	84:8	51:2	217:44	58:14	39:12	169:37	127:18	565:166
age(mean±SD)	74.8±11.2	67.0±9.8	58.1±12.4	62.5±11.1	68.1±10.2	66.9±10.5	67.5±10.1	63.6±11.8	62.3±11.2	64.6±10.7	64.6±10.8	67.4±10.0	49.9±19.5
Printing and allied industries *n=1316* (male:female)	1,067:249	84:0	0:94	35:6	23:0	130:5	80:2	233:44	82:13	51:15	213:55	136:15	579:215
age(mean±SD)	65.2±11.8	67.8±9.2	54.5±13.4	60.5±11.1	72.0±9.2	67.3±12.0	67.1±9.4	64.8±11.7	66.9±10.5	67.1±10.5	64.5±11.5	67.1±11.0	48.9±18.0
Chemicals, and chemical and allied products *n=3656* (male:female)	3,299:357	350:0	0:143	102:11	38:0	336:11	121:28	797:75	233:17	151:9	614:63	532:25	1,634:328
age(mean±SD)	66.5±11.4	69.9±9.4	52.4±12.2	63.1±11.3	70.6±9.1	68.4±11.2	65.2±8.92	63.9±8.2	64.2±8.8	67.5±9.6	66.4±11.6	68.9±10.2	51.5±18.9
Petroleum and coal products *n=360* (male:female)	339:21	33:0	0:7	12:0	3:0	36:2	19:0	82:5	20:3	16:0	68:3	50:1	147:17
age(mean±SD)	63.7±11.4	67.7±8.51	45.6±13.2	62.4±9.6	75.6±9.3	65.9±11.2	66.7±10.3	61.5±11.8	68.0±10.5	58.0±15.9	63.4±10.9	64.9±8.6	50.7±16.6
Plastic products, except otherwise classified *n=599* (male:female)	421:178	28:0	1:62	16:4	4:1	34:7	32:3	95:38	30:1	19:5	92:38	71:18	377:138
age(mean±SD)	62.4±11.1	63.8±7.8	58.2±10.7	56.8±8.8	67.8±8.5	65.9±12.3	61.5±10.8	61.0±11.6	60.8±11.9	61.7±9.7	64.5±11.7	64.4±9.5	48.7±16.6
Rubber products *n=316* (male:female)	248:68	18:0	0:22	8:3	6:1	35:0	14:1	58:14	25:3	11:6	40:14	33:4	136:51
age(mean±SD)	64.7±11.8	71.3±9.3	54.3±12.9	64.2±12.4	60.4±11.3	69.5±10.3	61.3±12.1	63.1±11.3	61.6±10.5	66.8±10.1	66.6±11.9	67.5±10.9	49.5±19.8
Leather tanning, leather products and fur *n=106* (male:female)	75:31	5:0	0:10	2:1	1:0	8:0	1:0	23:6	11:1	4:4	11:4	9:5	24:21
age(mean±SD)	61.3±11.1	69.6±9.1	48.8±11.4	70.6±4.2	–	64.3±14.7	–	60.1±11.4	64.9±7.3	59.8±10.0	62.4±9.5	62.5±9.8	50.3±19.9
Ceramic, stone and clay products *n=2167* (male:female)	1,878:289	139:0	4:72	45:4	28:1	196:14	88:1	441:70	159:23	77:14	323:56	378:34	1,071:244
age(mean±SD)	66.5±10.9	69.8±8.7	58.2±13.5	63.5±11.5	65.9±11.1	70.0±10.4	66.9±9.5	64.5±11.6	64.9±11.9	67.4±11.4	67.1±10.4	67.9±9.4	52.6±16.8
Iron and steel *n=3970* (male:female)	3,746:224	348:0	6:70	106:2	48:0	393:7	173:2	946:46	321:12	179:17	659:42	568:25	1,996:193
age(mean±SD)	66.1±10.6	69.1±8.7	54.0±11.1	64.5±10.4	68.1±9.0	68.9±10.1	65.7±9.5	63.6±11.4	64.3±9.94	66.8±10.5	66.4±10.4	69.0±9.37	50.9±17.7
Non-ferrous metals and products *n=1091* (male:female)	990:101	84:0	3:38	29:2	13:0	112:4	52:2	236:24	65:4	53:3	176:18	168:5	554:59
age(mean±SD)	66.3±10.9	68.9±8.25	55.6±11.7	64.8±11.1	60.3±10.1	68.1±11.0	66.1±10.6	65.1±11.9	64.2±8.8	67.4±9.8	65.5±10.6	69.5±10.0	49.4±17.2
Fabricated metal products *n=4614* (male:female)	3,823:791	279:0	3:192	93:13	36:8	342:29	223:9	1,015:193	307:31	178:44	750:203	598:68	2,871:728
age(mean±SD)	66.1±10.6	67.5±8.4	58.0±11.9	63.9±10.6	72.3±10.5	69.1±9.9	65.8±8.9	65.0±8.5	64.9±10.2	67.8±9.3	66.4±10.1	68.3±9.75	51.0±17.5
General purpose machinery *n=3992* (male:female)	3,546:446	306:0	6:149	122:8	51:2	377:14	156:4	889:90	281:12	152:23	682:97	524:47	2,328:403
age(mean±SD)	65.5±11.4	69.3±7.8	55.1±13.3	64.2±11.9	68.6±10.9	68.3±10.8	66.4±8.3	64.3±11.7	64.3±10.2	66.9±10.3	64.8±11.4	67.9±11.0	49.3±17.3
Electrical machinery, equipment and supplies *n=1497* (male:female)	1,153:344	98:0	2:100	51:12	19:2	125:10	55:3	262:81	65:14	49:13	258:66	169:43	663:241
age(mean±SD)	62.7±12.2	64.1±8.4	49.4±12.1	59.3±12.9	63.5±11.1	68.7±12.4	66.2±10.5	61.9±11.9	60.7±11.8	63.7±10.3	63.8±11.7	64.9±11.3	46.6±16.9
Information and communication electronics *n=783* (male:female)	585:198	58:0	1:77	28:7	9:1	65:4	29:3	119:39	28:8	38:10	129:22	81:27	455:151
age(mean±SD)	61.4±12.7	66.6±9.53	51.1±9.7	55.1±11.7	67.9±8.9	61.7±15.3	65±9.3	60.6±12.7	62.4±11.6	61.5±12.4	62.8±12.8	65.7±11.1	42.2±14.9
Electronic parts, devices and electronic circuits *n=837* (male:female)	521:316	37:0	0:104	27:9	9:2	60:6	20:1	116:69	31:10	33:18	120:71	68:26	652:267
age(mean±SD)	58.8±11.9	62.6±8.9	50.7±11.3	56.8±10.7	68.9±6.3	64.1±11.5	64.6±14.5	56.6±11.6	61.5±11.1	61.7±9.1	58.6±11.9	62.7±10.6	42.3±14.8
Transportation equipment *n=3666* (male:female)	3,306:362	251:0	5:103	91:5	45:8	368:14	140:6	852:58	281:7	160:20	550:96	562:44	2,225:313
age(mean±SD)	66.2±11.2	68.9±8.7	54.1±11.8	62.8±10.8	69.5±10.1	69.5±10.8	66.9±9.2	65.2±11.7	64.9±10.0	67.1±11.2	66.0±11.2	67.33±10.5	48.7±17.8
Precision machinery *n=487* (male:female)	386:101	29:0	2:41	12:0	1:0	41:2	21:0	96:19	38:2	21:2	76:25	49:10	279:84
age(mean±SD)	62.2±11.5	65.5±8.8	54.3±12.5	55.2±9.5	–	65.6±10.0	68.9±12.2	60.4±13.3	62.5±8.2	64.1±12.6	62.7±10.0	64.4±9.9	46.2±17.2
Miscellaneous manufacturing industries *n=952* (male:female)	659:293	46:0	0:83	17:8	9:5	72:11	31:1	180:80	46:6	24:11	144:60	90:28	357:215
age(mean±SD)	66.0±11.7	71.7±10.7	56.5±13.1	61.1±14.6	72.3±6.3	68.6±11.4	6.9±9.4	66.9±11.2	66.9±11.2	67.3±12.5	66.4±10.4	68.9±10.7	54.8±19.3

In columns that included only one case, age was not disclosed to prevent identifying individuals.

表１　製造業従事者のベースライン特性

Industry category	Brinkman Index†		Alcohol (g/day)	
	Median (IQR‡25%:75%)		Median (IQR‡25%:75%)	
	case	control	case	control
All	0(0:660)	0(0:125)	0(0:45.0)	0(0:0)
Food	0(0:350)	0(0:0)	0(0:35.0)	0(0:0)
Beverages, tobacco and feed	0(0:720)	0(0:60)	0(0:72.0)	0(0:0)
Textile mill products	0(0:440)	0(0:0)	0(0:44.0)	0(0:0)
Clothes and other textiles	0(0:0)	0(0:0)	0(0:0)	0(0:0)
Lumber and wood products, except furniture	0(0:740)	0(0:150)	0(0:74.0)	0(0:0)
Furniture and fixtures	0(0:700)	0(0:150)	0(0:70.0)	0(0:0)
Pulp, paper and paper products	0(0:690)	0(0:200)	0(0:69.0)	0(0:40.0)
Printing and allied industries	0(0:680)	0(0:102)	0(0:68.0)	0(0:4.0)
Chemicals, and chemical and allied products	0(0:750)	0(0:240)	0(0:75.0)	0(0:80.0)
Petroleum and coal products	285(0:740)	0(0:250)	28.5(0:74.0)	0(0:11.5)
Plastic products, except otherwise classified	0(0:600)	0(0:220)	0(0:60.0)	0(0:60)
Rubber products	0(0:640)	0(0:0)	0(0:64.0)	0(0:0)
Leather tanning, leather products and fur	0(0:440)	0(0:0)	0(0:44.0)	0(0:0)
Ceramic, stone and clay products	0(0:780)	0(0:260)	0(0:78.0)	0(0:10.5)
Iron and steel	0(0:720)	0(0:135)	0(0:72.0)	0(0:0)
Non-ferrous metals and products	0(0:740)	0(0:350)	15.0(0:74.0)	0(0:24.0)
Fabricated metal products	15(0:735)	0(0:200)	0(0:73.5)	0(0:30.0)
General purpose machinery	0(0:720)	0(0:202)	0(0:72.0)	0(0:55.0)
Electrical machinery, equipment and supplies	0(0:660)	0(0:560)	0(0:66.0)	0(0:0)
Information and communication electronics	0(0:540)	0(0:0)	0(0:54.0)	0(0:0)
Electronic parts, devices and electronic circuits	0(0:470)	0(0:60)	0(0:47.0)	0(0:0)
Transportation equipment	0(0:765)	0(0:200)	0(0:76.5)	0(0:60.0)
Precision machinery	0(0:600)	0(0:210)	0(0:60.0)	0(0:50.0)
Miscellaneous manufacturing industries	0(0:510)	0(0:320)	0(0:51.0)	0(0:0)

†Brinkman Index: the number of cigerettes smoked per day multiplied by the number of years smoked.

‡IQR: Intercuartile range.

表2 各製造業従事者の喫煙量、飲酒量の分布

Table 3. Odds ratio of each manufacturing industry category to cancer

Industrial category		Prostate	Breast	Kidney	Ureter	Bladder	Esophagus	Stomach	Liver	Pancreas	Colon	Lung
Food (reference)		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)	1.00(ref)
		–	–	–	–	–	–	–	–	–	–	–
Beverages, tobacco and feed	OR(95%CI)	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)	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)
	p–value	0.207	0.359	0.802	0.145	0.966	0.932	0.686	0.834	0.562	0.446	0.163
Textile mill products	OR(95%CI)	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)	1.03(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)
	p–value	0.583	0.562	0.057	0.040*	0.827	0.873	0.803	0.300	0.779	0.978	0.765
Clothes and other textiles	OR(95%CI)	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)	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)
	p–value	0.300	0.016*	0.355	0.067	0.801	0.237	0.803	0.766	0.884	0.191	0.596
Lumber and wood products, except furniture	OR(95%CI)	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)	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)
	p–value	0.014*	0.220	0.698	0.581	0.005**	0.000**	0.000**	0.000**	0.010*	0.001**	0.072
Furniture and fixtures	OR(95%CI)	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)	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)
	p–value	0.400	0.219	0.164	0.112	0.731	0.014*	0.454	0.018*	0.037*	0.223	0.437
Pulp, paper and paper products	OR(95%CI)	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)	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)
	p–value	0.266	0.772	0.355	0.162	0.524	0.107	0.724	0.182	0.290	0.639	0.312
Printing and allied industries	OR(95%CI)	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)	1.26(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)
	p–value	0.353	0.053	0.016*	0.014*	0.008**	0.148	0.766	0.838	0.351	0.000**	0.997
Chemicals, and chemical and allied products	OR(95%CI)	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)	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)
	p–value	0.040*	0.04*	0.030*	0.909	0.795	0.002**	0.398	0.174	0.234	0.086	0.411
Petroleum and coal products	OR(95%CI)	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)	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)
	p–value	0.009**	0.770	0.045*	0.982	0.032*	0.605	0.011**	0.787	0.612	0.006**	0.029**
Plastic products, except otherwise classified	OR(95%CI)	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)	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)
	p–value	0.218	0.050	0.189	0.586	0.216	0.835	0.485	0.054	0.204	0.446	0.623
Rubber products	OR(95%CI)	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)	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)
	p–value	0.779	0.278	0.102	0.018*	0.196	0.949	0.503	0.294	0.535	0.680	0.767
Leather tannning, leather products and fur	OR(95%CI)	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)	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)
	p–value	0.319	0.406	0.274	0.407	0.143	0.341	0.015*	0.019**	0.012**	0.243	0.028*
Ceramic, stone and clay products	OR(95%CI)	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)	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)
	p–value	0.286	0.704	0.720	0.260	0.875	0.003**	0.400	0.771	0.075	0.538	0.008**
Iron and steel	OR(95%CI)	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)	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)
	p–value	0.126	0.473	0.387	0.266	0.423	0.006**	0.213	0.540	0.898	0.294	0.615
Non–ferrous metals and products	OR(95%CI)	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)	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)
	p–value	0.288	0.001**	0.149	0.520	0.063	0.459	0.213	0.488	0.410	0.110	0.267
Fabricated metal products	OR(95%CI)	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)	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)
	p–value	0.013*	0.030*	0.236	0.290	0.002**	0.004**	0.096	0.005**	0.017*	0.439	0.011*
General–purpose mechinery	OR(95%CI)	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)	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)
	p–value	0.726	0.237	0.055	0.286	0.675	0.000**	0.953	0.135	0.120	0.126	0.709
Electrical machinery, equipment and supplies	OR(95%CI)	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)	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)
	p–value	0.002**	0.069	0.000**	0.011*	0.003**	0.917	0.000**	0.991	0.368	0.000**	0.000**
Information and communication electronics	OR(95%CI)	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)	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)
	p–value	0.001**	0.009**	0.000**	0.043*	0.001**	0.616	0.082	0.467	0.001**	0.001**	0.000**
Electronic parts, devices and electronic circuits	OR(95%CI)	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)	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)
	p–value	0.765	0.329	0.001**	0.120	0.136	0.030*	0.139	0.290	0.051	0.001**	0.344
Transportation equipment	OR(95%CI)	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)	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)
	p–value	0.302	0.961	0.873	0.140	0.746	0.000**	0.295	0.627	0.398	0.644	0.174
Precision machinery	OR(95%CI)	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)	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)
	p–value	0.703	0.961	0.652	0.132	0.593	0.269	0.314	0.627	0.987	0.043*	0.894
Miscellaneous manufacturing industries	OR(95%CI)	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)	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)
	p–value	0.209	0.185	0.516	0.176	0.686	0.031**	0.199	0.039*	0.031*	0.177	0.299

Odds ratios for 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.

p–values <0.01** or <0.05* were considered to be statistically significant.

表 3　製造業 40,370 例を用いたの癌リスク（オッズ比）

Cancer site(ICD-10)				
Prsotate(C619)				
Number of registerd		n<1000	1000≤n<2000	2000≤n
Total	n(%)	9,523(37.44)	8,232(32.36)	7,680(30.19)
Gender	n(%)			
	Male	9,523(100.00)	8,232(100.00)	7,680(30.19)
	Female	–	–	–
Age	Median(IQR†)	74(68:79)	73(68:78)	70(66:75)
TNMstage	n(%)			
Stage1		3,113(32.69)	2,415(29.34)	2,305(30.01)
Stage2		3,732(39.19)	3,580(43.49)	3,385(44.08)
Stage3		1,054(11.07)	897(10.90)	1,060(13.80)
Stage4		1,624(17.05)	1,340(16.28)	930(12.11)

Bladder(C670/679)				
Number of registerd		n<400	400≤n<1000	1000≤n
Total	n(%)	1,386(28.73)	2,924(60.61)	514(10.66)
Gender	n(%)			
	Male	1,079(77.85)	2,311(79.04)	400(77.82)
	Female	307(22.15)	613(20.96)	114(22.18)
Age	Median(IQR†)	75(66:82)	72(64:79)	72(64:79)
TNMstage	n(%)			
Stage1		738(53.25)	1,548(52.94)	249(48.44)
Stage2		327(23.59)	650(22.23)	140(27.24)
Stage3		146(10.53)	390(13.34)	57(11.09)
Stage4		175(12.63)	336(11.49)	68(13.23)

Stomach(C160/169)				
Number of registerd		n<1000	1000≤n<3000	3000≤n
Total	n(%)	7,182(18.89)	16,859(44.35)	13,976(36.76)
Gender	n(%)			
	Male	5,061(70.47)	12,019(71.29)	9,864(70.58)
	Female	2,121(29.53)	4,840(28.71)	4,112(29.42)
Age	Median(IQR†)	73(65:81)	71(64:78)	69(62:76)
TNMstage	n(%)			
Stage1		3,681(51.25)	9,431(55.94)	8,719(62.39)
Stage2		847(11.79)	1,936(11.48)	1,272(9.10)
Stage3		718(10.00)	1,704(10.11)	1,495(10.70)
Stage4		1,936(26.96)	3,788(22.47)	2,490(17.82)

Pancreas(C250/259)				
Number of registerd		n<400	400≤n<1000	1000≤n
Total	n(%)	5,499(54.25)	2,571(25.36)	2,067(20.39)
Gender	n(%)			
	Male	3,044(55.36)	1,431(55.66)	1,206(58.35)
	Female	2,455(44.64)	1,140(44.34)	861(41.65)
Age	Median(IQR†)	73(65:81)	71(63:78)	68(61:74)
TNMstage	n(%)			
Stage1		555(10.09)	171(6.65)	181(8.90)
Stage2		896(16.29)	387(15.05)	461(23.30)
Stage3		823(14.97)	521(20.26)	390(18.87)
Stage4		3,225(58.65)	1,492(58.03)	1,032(49.93)

Breast(C500/509)				
Number of registerd		n<1000	1000≤n<3000	3000≤n
Total	n(%)	9,044(31.62)	9,860(34.48)	9,695(33.90)
Gender	n(%)			
	Male	58(0.64)	52(0.53)	28(0.29)
	Female	8,986(31.57)	9,808(99.47)	9,667(99,71)
Age	Median(IQR†)	61(49:72)	59(49:69)	55(46:65)
TNMstage	n(%)			
Stage1		3,985(44.06)	4,114(41.72)	4,357(44.94)
Stage2		3,409(37.69)	4,080(41.38)	3,772(38.91)
Stage3		980(10.84)	1,048(10.63)	1,027(10.59)
Stage4		670(6.41)	618(6.27)	539(5.56)

Kidney(C649)				
Number of registerd		n<400	400≤n<1000	1000≤n
Total	n(%)	764(15.32)	1,749(35.07)	2,474(49.61)
Gender	n(%)			
	Male	557(72.91)	1,246(71.24)	1,795(72.55)
	Female	207(27.09)	503(28.76)	679(27.45)
Age	Median(IQR†)	72(63:81)	70(61:77)	66(57:74)
TNMstage	n(%)			
Stage1		455(59.55)	1,148(65.64)	1,727(69.81)
Stage2		64(8.38)	125(7.15)	134(5.42)
Stage3		75(9.82)	146(8.35)	206(8.33)
Stage4		170(22.25)	330(18.87)	407(16.45)

Esophagus(C150/159)				
Number of registerd		n<400	400≤n<1000	1000≤n
Total	n(%)	3,450(36.96)	2,032(21.77)	3,853(41.27)
Gender	n(%)			
	Male	2,916(36.66)	1,706(21.45)	3,333(41.90)
	Female	534(15.48)	326(16.04)	520(13.50)
Age	Median(IQR†)	69(62:76)	68(63:75)	67(61:73)
TNMstage	n(%)			
Stage1		1,020(29.57)	682(33.56)	1,334(34.62)
Stage2		581(16.84)	340(16.73)	522(13.55)
Stage3		933(27.04)	574(28.25)	1,181(30.65)
Stage4		916(26.55)	436(21.46)	816(21.18)

Liver(C220)				
Number of registerd		n<400	400≤n<1000	1000≤n
Total	n(%)	3,385(35.66)	2,673(28.92)	3,434(29.15)
Gender	n(%)			
	Male	2,359(69.69)	1,900(71.08)	2,433(70.85)
	Female	1,026(30.31)	773(28.92)	1,001(29.15)
Age	Median(IQR†)	71(64:78)	70(64:77)	69(63:74)
TNMstage	n(%)			
Stage1		1,328(39.23)	1,101(41.19)	1,365(39.75)
Stage2		890(26.29)	710(26.56)	960(27.96)
Stage3		693(20.47)	593(22.18)	779(22.68)
Stage4		474(14.00)	269(10.06)	330(9.61)

Colon(C180/189,C199,C209)				
Number of registerd		n<1000	1000≤n<2000	2000≤n
Total	n(%)	6,654(26.18)	8,619(33.90)	10,150(39.92)
Gender	n(%)			
	Male	3,688(55.41)	4,770(55.34)	5,547(54.64)
	Female	2,968(44.59)	3,849(44.66)	4,604(45.36)
Age	Median(IQR†)	73(64:81)	70(63:78)	69(61:76)
TNMstage	n(%)			
Stage1		1,882(28.28)	2,278(26.43)	3,005(29.61)
Stage2		1430(21.49)	1,960(22.74)	1,943(19.14)
Stage3		1,613(24.24)	2,486(28.84)	3,217(31.69)
Stage4		1,729(25.98)	1,895(21.99)	1,985(19.56)

Lung(C340/349)				
Number of registerd		n<1000	1000≤n<3000	3000≤n
Total	n(%)	8,148(23.49)	16,726(48.22)	9,816(28.30)
Gender	n(%)			
	Male	5,668(69.56)	11,686(69.87)	6,645(67.60)
	Female	2,480(30.44)	5,040(30.13)	3,171(32.30)
Age	Median(IQR†)	75(67:82)	72(64:78)	69(62:75)
TNMstage	n(%)			
Stage1		2,152(26.41)	5,563(33.26)	4,206(42.85)
Stage2		562(6.90)	1,135(6.79)	835(8.51)
Stage3		1,595(19.58)	3,454(20.65)	1,912(19.48)
Stage4		3,839(47.12)	6,574(39.30)	2,863(29.17)

Because of rounding, percentages may not total 100.

†IQR: Interquartile range.

表 4　登録施設規模による登録症例のベースライン特性

Cancer category	High volume	Others	p=
Prostate(C619)	9571	15119	
Gender(male:female)	9571:0	15119:0	-
Age(median:IQR[§])	71.2(66.1:75.9)	73.1(67.9:78.0)	0.000[‡]
Priod of diagnosis(1:2:3:4:5)	2:12:67:3062:6428	4:18:238:3923:10936	
Stage(1:2:3:4)	2861:4364:1166:1180	4511:6126:1795:2687	
Kidney(C649)	1739	3090	
Gender(male:female)	1258:481	2230:860	0.898
Age(median:IQR[§])	65.4(56.5:72.4)	65.3(56.6:72.5)	0.000[‡]
Priod of diagnosis(1:2:3:4:5)	0:2:29:684:1024	0:9:50:707:2324	
Stage(1:2:3:4)	1227:91:131:290	1979:217:289:605	
Bladder(C670/679)	1363	3372	
Gender(male:female)	1061:302	2655:717	0.498
Age(median:IQR[§])	74.2(66.2:80.9)	73.8(66.1:80.3)	0.047[†]
Priod of diagnosis(1:2:3:4:5)	0:1:7:450:905	2:6:59:852:2453	
Stage(1:2:3:4)	647:371:189:156	1821:732:401:418	
Esophagus(C150/159)	3204	5449	
Gender(male:female)	2766:438	4611:838	0.030[†]
Age(median:IQR[§])	70.5(64.1:76.6)	68.4(63.1:74.3)	0.000[‡]
Priod of diagnosis(1:2:3:4:5)	0:3:182:1216:1803	0:29:247:1462:3711	
Stage(1:2:3:4)	1114:434:985:671	1501:878:1638:1432	
Stomach(C160/169)	12636	21969	
Gender(male:female)	8920:3716	15585:6384	0.492
Age(median:IQR[§])	70.8(63.8:77.1)	70.9(63.8:77.1)	0.000[‡]
Priod of diagnosis(1:2:3:4:5)	3:125:961:4505:7042	6:108:935:5886:15034	
Stage(1:2:3:4)	7379:1272:1495:2490	11321:2651:2369:5628	
Liver(C220)	3666	5454	
Gender(male:female)	2596:1070	3825:1629	0.485
Age(median:IQR[§])	71.5(64.4:77.4)	73.3(65.8:79.3)	0.000[†]
Priod of diagnosis(1:2:3:4:5)	6:28:209:1310:2113	2:14:120:1597:3721	
Stage(1:2:3:4)	1485:1019:814:348	2041:1477:1223:713	
Pancreas(C250/259)	3442	6197	
Gender(male:female)	1961:1481	3440:2757	0.166
Age(median:IQR[§])	69.6(63.0:75.6)	69.6(63.1:75.9)	0.000[†]
Priod of diagnosis(1:2:3:4:5)	1:2:144:1204:2091	0:17:180:1430:4570	
Stage(1:2:3:4)	200:691:733:1818	424:968:957:3848	
Colon(C180/189/199/209)	9493	15465	
Gender(male:female)	5181:4312	8554:6911	0.257
Age(median:IQR[§])	70.9(63.1:77.7)	72.6(65.1:79.6)	0.000[†]
Priod of diagnosis(1:2:3:4:5)	16:141:603:3483:5250	3:57:690:3826:10889	
Stage(1:2:3:4)	2877:1837:2949:1830	4096:3327:4316:3726	
Breast(C500/509)	9694	17955	
Gender(male:female)	28:9666	107:17848	0.000[‡]
Age(median:IQR[§])	57.3(47.1:67.1)	60.9(50.0:71.6)	0.000[†]
Priod of diagnosis(1:2:3:4:5)	3:47:530:3381:5733	22:225:1000:4807:11901	
Stage(1:2:3:4)	4356:3772:1027:539	7463:7237:1993:1262	
Lung(C340/349)	12373	19788	
Gender(male:female)	8415:3958	13930:5858	0.000[‡]
Age(median:IQR[§])	70.5(63.6:76.5)	72.7(65.8:79.1)	0.000[†]
Priod of diagnosis(1:2:3:4:5)	3:67:826:4499:6978	8:98:951:4941:13790	
Stage(1:2:3:4)	4629:1081:2643:4020	5105:1309:4245:9129	

p-values <0.01[**] or <0.05[*] were considered to be statistically significant.

[§]IQR: Interquartile range.

表5 Propensity score matching前の症例分布

Table 2. Baseline characteristics of cases of high volume center and matched pair from others.

Cancer category	Cases in high volume	Matched cases	p*
Prostate(C619)	9571	9571	
Gender(male:female)	9571:0	9571:0	-
Age(median:IQR[$])	71.2(66.1-75.9)	71.3(66.2-76.2)	0.329
Priod of diagnosis(1:2:3:4:5)	2:12:67:3062:6428	4:16:196:2793:6562	
Stage(1:2:3:4)	2861:4364:1166:1180	3149:4131:972:1319	
Kidney(C649)	1739	1739	
Gender(male:female)	1258:481	1256:483	0.940
Age(median:IQR[$])	65.4(56.5-72.4)	64.8(55.7-72.7)	0.721
Priod of diagnosis(1:2:3:4:5)	0:2:29:684:1024	0:9:50:592:1088	
Stage(1:2:3:4)	1227:91:131:290	1181:138:145:275	
Bladder(C670-679)	1363	1363	
Gender(male:female)	1061:302	1064:302	0.890
Age(median:IQR[$])	74.2(68.2-80.9)	74.5(68.8-80.4)	0.687
Priod of diagnosis(1:2:3:4:5)	0:1:7:450:905	0:0:29:396:938	
Stage(1:2:3:4)	647:371:189:156	679:316:176:192	
Esophagus(C150-159)	3204	3204	
Gender(male:female)	2766:438	2771:433	0.855
Age(median:IQR[$])	70.5(64.1-76.6)	68.6(62.5-74.8)	0.569
Priod of diagnosis(1:2:3:4:5)	0:3:182:1216:1803	0:29:215:1060:1900	
Stage(1:2:3:4)	1114:434:985:671	1071:550:883:700	
Stomach(C160-169)	12636	12636	
Gender(male:female)	8920:3716	8999:3637	0.274
Age(median:IQR[$])	70.8(63.8-77.1)	70.8(63.5-77.2)	0.364
Priod of diagnosis(1:2:3:4:5)	3:125:961:4505:7042	6:108:884:4380:7258	
Stage(1:2:3:4)	7379:1272:1495:2490	7493:1496:1201:2446	
Liver(C220)	3666	3666	
Gender(male:female)	2596:1070	2583:1083	0.739
Age(median:IQR[$])	71.5(64.4-77.4)	71.6(63.9-77.7)	0.667
Priod of diagnosis(1:2:3:4:5)	6:28:209:1310:2113	2:14:120:1405:2125	
Stage(1:2:3:4)	1485:1019:814:348	1520:1055:711:380	
Pancreas(C250-259)	3442	3442	
Gender(male:female)	1961:1481	1991:1451	0.465
Age(median:IQR[$])	69.6(63.0-75.8)	69.0(62.6-75.8)	0.627
Priod of diagnosis(1:2:3:4:5)	1:2:144:1204:2091	0:15:170:1056:2201	
Stage(1:2:3:4)	200:691:733:1818	306:629:585:1922	
Colon(C180-189-199-209)	9493	9493	
Gender(male:female)	5181:4312	5238:4255	0.406
Age(median:IQR[$])	70.9(63.1-77.7)	70.9(63.3-77.8)	0.703
Priod of diagnosis(1:2:3:4:5)	16:141:603:3483:5250	3:57:690:3392:5351	
Stage(1:2:3:4)	2877:1837:2949:1830	2754:2156:2616:1967	
Breast(C500-509)	9694	9694	
Gender(male:female)	28:9666	26:9668	0.785
Age(median:IQR[$])	57.3(47.1-67.1)	57.1(47.4-66.9)	0.958
Priod of diagnosis(1:2:3:4:5)	3:47:530:3381:5733	18:155:654:2731:6136	
Stage(1:2:3:4)	4356:3772:1027:539	4345:3863:929:557	
Lung(C340-349)	12373	12373	
Gender(male:female)	8415:3958	8530:3843	0.116
Age(median:IQR[$])	70.5(63.6-76.5)	70.5(63.7-76.7)	0.173
Priod of diagnosis(1:2:3:4:5)	3:67:826:4499:6978	8:98:926:3789:7552	
Stage(1:2:3:4)	4629:1081:2643:4020	3:67:826:4499:6978	

*p-values <0.01** or <0.05* were considered to be statistically significant.

[$]IQR: Interquartile range.

表6 Propensity score matching後の症例分布

Cancer category	Gender		Age	Brinkman Index†	Alcohol
	Male(%)	Female(%)	(median;IQR‡)	(median;IQR‡)	(g/day)
Total	5,241(59.60)	3,553(40.40)	68(59;75)	0(0;620)	0(0;180)
Prostate(C619)	542(10.34)	0(0)	65(60;74)	40(0;675)	0(0;495)
Kidney(C649)	268(27.00)	132(33.00)	64(54;72)	0(0;540)	0(0;300)
Bladder(C670/679)	450(75.76)	144(24.24)	70(60;77)	20(0;730)	0(0;500)
Esophagus(C150/159)	252(85.42)	43(14.58)	68(60;74)	350(0;860)	0(0;600)
Stomach(C160/169)	855(65.77)	445(34.23)	69(60;76)	0(0;620)	0(0;300)
Liver(C220)	331(69.68)	144(30.32)	68(61;75)	0(0;600)	0(0;0)
Pancreas(C250/259)	226(50.79)	219(49.21)	71(62;78)	0(0;570)	0(0;0)
Colon(C180/189,199,209)	1,320(58.07)	953(41.93)	68(60;76)	0(0;540)	0(0;84)
Breast(C500/509)	6(0.65)	918(99.35)	58(47;68)	0(0;0)	0(0;0)
Lung(C340/349)	991(64.10)	555(35.90)	69(61;76)	300(0;900)	0(0;530)

Because of rounding, percentages may not total 100.

†Brinkman Index: the number of cigerettes smoked per day multiplied by the number of years smoked.

‡IQR: Interquartile range.

表7 突合全症例のベースライン特性

	Gender		Age	Brinkman Index†	Alcohol
	Male(%)	Female(%)	(median;IQR‡)	(median;IQR‡)	(g/day)
Total	3,431(74.10)	1,199(25.90)	65(56;72)	100(0;760)	0(0;620)
Cancer category					
Prostate(C619)	409(100.00)	0(0)	64(58;71)	100(0;680)	0(0;620)
Kidney(C649)	207(83.47)	41(16.53)	61(50;70)	120(0;640)	0(0;540)
Bladder(C670/679)	330(87.53)	47(12.47)	67(57;75)	220(0;780)	0(0;660)
Esophagus(C150/159)	166(92.22)	14(7.78)	66(59;73)	432(0;970)	375(0;900)
Stomach(C160/169)	573(80.82)	136(19.18)	66(57;73)	165(0;760)	0(0;660)
Liver(C220)	191(86.04)	31(13.96)	66(60;73)	9(0;660)	0(0;600)
Pancreas(C250/259)	127(69.78)	55(30.22)	68(60;74)	0(0;840)	0(0;620)
Colon(C180/189/199/209)	809(75.82)	258(24.18)	65(57;72)	160(0;700)	0(0;600)
Breast(C500/509)	3(0.69)	430(99.31)	52(46;62)	0(0;0)	0(0;0)
Lung(C340/349)	616(76.71)	187(23.29)	66(58;73)	550(0;1000)	150(0;860)
Sector of indsutry					
Primary	43(69.35)	19(30.65)	76(68;82)	255(0;900)	0(0;880)
Secondary	1,746(85.05)	307(14.95)	66(58;74)	280(0;820)	0(0;700)
Tertiary	1,642(65.29)	873(34.71)	63(54;70)	0(0;700)	0(0;555)

Because of rounding, percentages may not total 100.

†Brinkman Index: the number of cigerettes smoked per day multiplied by the number of years smoked.

‡IQR: Interquartile range.

表8 職歴のある突合症例のベースライン特性

Cancer site(ICD-10)

Prostate(C619)

Sector of industry		Primary	Secondary	Tertiary
Total	n(%)	1(0.5)	93(46.50)	106(53.00)
Gender	n(%)			
	Male	1(0.5)	93(46.50)	106(53.00)
	Female	–	–	–
Age	Median(IQR†)	79(69:84)	67(59:74)	64(55:72)
TNMstage	n(%)			
Stage1		0(0.00)	48(51.61)	42(39.62)
Stage2		1(100.00)	29(31.18)	33(31.13)
Stage3		0(0.00)	4(4.30)	7(6.60)
Stage4		0(0)	12(12.90)	24(22.64)
Brinkman Index		490(–:–)	230(0:620)	180(0:720)
Alcohol (g/day)		60(–:–)	80(0:600)	55(0:660)

Kidney(C649)

Sector of industry		Primary	Secondary	Tertiary
Total	n(%)	15(0.72)	829(40.05)	1,226(59.23)
Gender	n(%)			
	Male	12(80.00)	692(83.47)	763(62.23)
	Female	3(20.00)	137(16.53)	463(37.77)
Age	Median(IQR†)	79(69:84)	67(59:74)	64(55:72)
TNMstage	n(%)			
Stage1		2(13.33)	352(42.46)	494(40.29)
Stage2		7(46.67)	164(19.78)	247(20.15)
Stage3		4(26.67)	131(15.80)	184(15.01)
Stage4		2(13.33)	182(21.95)	301(24.55)
Brinkman Index		560(0:880)	460(0:840)	240(0:740)
Alcohol (g/day)		0(0:670)	360(0:800)	55(0:640)

Bladder(C670/679)

Sector of industry		Primary	Secondary	Tertiary
Total	n(%)	1(1.64)	32(52.46)	28(45.90)
Gender	n(%)			
	Male	1(100.00)	29(90.62)	25(85.29)
	Female	0(0)	3(9.38)	3(10.71)
Age	Median(IQR†)	79(69:84)	67(59:74)	64(55:72)
TNMstage	n(%)			
Stage1		0(0)	19(59.38)	13(46.43)
Stage2		0(0)	10(31.25)	8(28.57)
Stage3		1(100)	2(6.25)	2(7.14)
Stage4		0(0)	1(3.12)	5(17.86)
Brinkman Index		0(–:–)	650(275:940)	640(180:820)
Alcohol (g/day)		0(–:–)	540(0:812)	527(160:780)

Esophagus(C150/C159)

Sector of industry		Primary	Secondary	Tertiary
Total	n(%)	0(0)	17(47.22)	19(52.78)
Gender	n(%)			
	Male	0(0)	15(66.24)	18(94.74)
	Female	0(0)	2(11.76)	1(5.26)
Age	Median(IQR†)	79(69:84)	67(59:74)	64(55:72)
TNMstage	n(%)			
Stage1		0(0)	5(29.41)	10(52.63)
Stage2		0(0)	2(11.76)	0(0)
Stage3		0(0)	3(17.65)	5(26.32)
Stage4		0(0)	7(41.18)	4(21.05)
Brinkman Index		–	900(400:1050)	600(30:800)
Alcohol (g/day)		–	800(412:980)	400(0:756)

Stomach(C160/169)

Sector of industry		Primary	Secondary	Tertiary
Total	n(%)	4(1.65)	110(45.45)	128(52.89)
Gender	n(%)			
	Male	4(100.00)	103(93.64)	95(74.22)
	Female	0(0)	7(6.36)	33(25.78)
Age	Median(IQR†)	79(69:84)	67(59:74)	64(55:72)
TNMstage	n(%)			
Stage1		1(25.00)	75(68.18)	71(55.47)
Stage2		2(50.00)	15(13.64)	19(14.84)
Stage3		0(0)	6(5.45)	9(7.03)
Stage4		1(25.00)	14(12.73)	29(22.66)
Brinkman Index		670(355:900)	620(315:980)	198(0:740)
Alcohol (g/day)		355(35:870)	540(0:920)	112(0:720)

Liver(C220)

Sector of industry		Primary	Secondary	Tertiary
Total	n(%)	0(0)	30(42.86)	40(57.14)
Gender	n(%)			
	Male	0(0)	28(93.33)	26(65.00)
	Female	0(0)	2(6.67)	14(35.00)
Age	Median(IQR†)	–	65(59:71)	67(61:75)
TNMstage	n(%)			
Stage1		0(0)	11(36.67)	15(37.50)
Stage2		0(0)	9(30.00)	7(17.50)
Stage3		0(0)	5(16.67)	10(25.00)
Stage4		0(0)	5(16.67)	8(20.00)
Brinkman Index		–	395(180:820)	120(0:830)
Alcohol (g/day)		–	370(0:680)	0(0:830)

Pancreas(C250/259)

Sector of industry		Primary	Secondary	Tertiary
Total	n(%)	0(0)	31(45.59)	37(54.41)
Gender	n(%)			
	Male	0(0)	28(90.32)	17(45.95)
	Female	0(0)	3(9.68)	20(54.05)
Age	Median(IQR†)	79(69:84)	67(59:74)	64(55:72)
TNMstage	n(%)			
Stage1		0(0)	2(6.45)	4(10.81)
Stage2		0(0)	5(16.13)	5(13.51)
Stage3		0(0)	5(16.13)	2(5.41)
Stage4		0(0)	19(61.29)	26(70.27)
Brinkman Index		–	500(0:1050)	0(0:720)
Alcohol (g/day)		–	460(0:900)	0(0:320)

Colon(C180/189,C199,C209)

Sector of industry		Primary	Secondary	Tertiary
Total	n(%)	4(1.32)	121(40.07)	177(58.61)
Gender	n(%)			
	Male	3(75.00)	100(82.64)	119(67.23)
	Female	1(25.00)	21(17.36)	58(32.77)
Age	Median(IQR†)	75(60:82)	66(59:73)	65(57:73)
TNMstage	n(%)			
Stage1		0(0)	33(27.27)	50(28.25)
Stage2		2(50.00)	31(25.62)	44(24.86)
Stage3		2(50.00)	30(24.79)	43(24.29)
Stage4		0(0)	27(22.31)	40(22.60)
Brinkman Index		280(0:720)	340(0:760)	240(0:697)
Alcohol (g/day)		0(0:440)	300(0:645)	100(0:580)

Breast(C500/509)

Sector of industry		Primary	Secondary	Tertiary
Total	n(%)	1(0.57)	42(24.00)	132(75.43)
Gender	n(%)			
	Male	0(0)	0(0)	1(0.76)
	Female	1(0.57)	42(24.14)	131(99.24)
Age	Median(IQR†)	50(–:–)	60(46:72)	52(46:63)
TNMstage	n(%)			
Stage1		1(100.00)	14(33.33)	63(47.73)
Stage2		0(0)	19(45.24)	54(40.91)
Stage3		0(0)	5(11.90)	11(8.33)
Stage4		0(0)	4(9.52)	4(3.03)
Brinkman Index		0(–:–)	0(0:0)	0(0:0)
Alcohol (g/day)		0(–:–)	0(0:0)	0(0:0)

Lung(C340/349)

Sector of industry		Primary	Secondary	Tertiary
Total	n(%)	2(0.66)	119(39.27)	182(60.07)
Gender	n(%)			
	Male	2(100)	107(89.92)	129(70.88)
	Female	0(0)	12(10.08)	53(29.12)
Age	Median(IQR†)	80(73:87)	69(62:76)	66(59:73)
TNMstage	n(%)			
Stage1		0(0)	40(33.61)	67(36.81)
Stage2		1(50.00)	7(5.88)	10(5.49)
Stage3		1(50.00)	37(31.09)	44(24.18)
Stage4		0(0)	35(29.41)	61(33.52)
Brinkman Index		905(–:–)	800(460:1060)	705(200:1000)
Alcohol (g/day)		885(–:–)	720(0:980)	475(0:920)

Because of rounding, percentages may not total 100.

†IQR: Interquartile range.

表 9　産業ごとの診断時病期分布

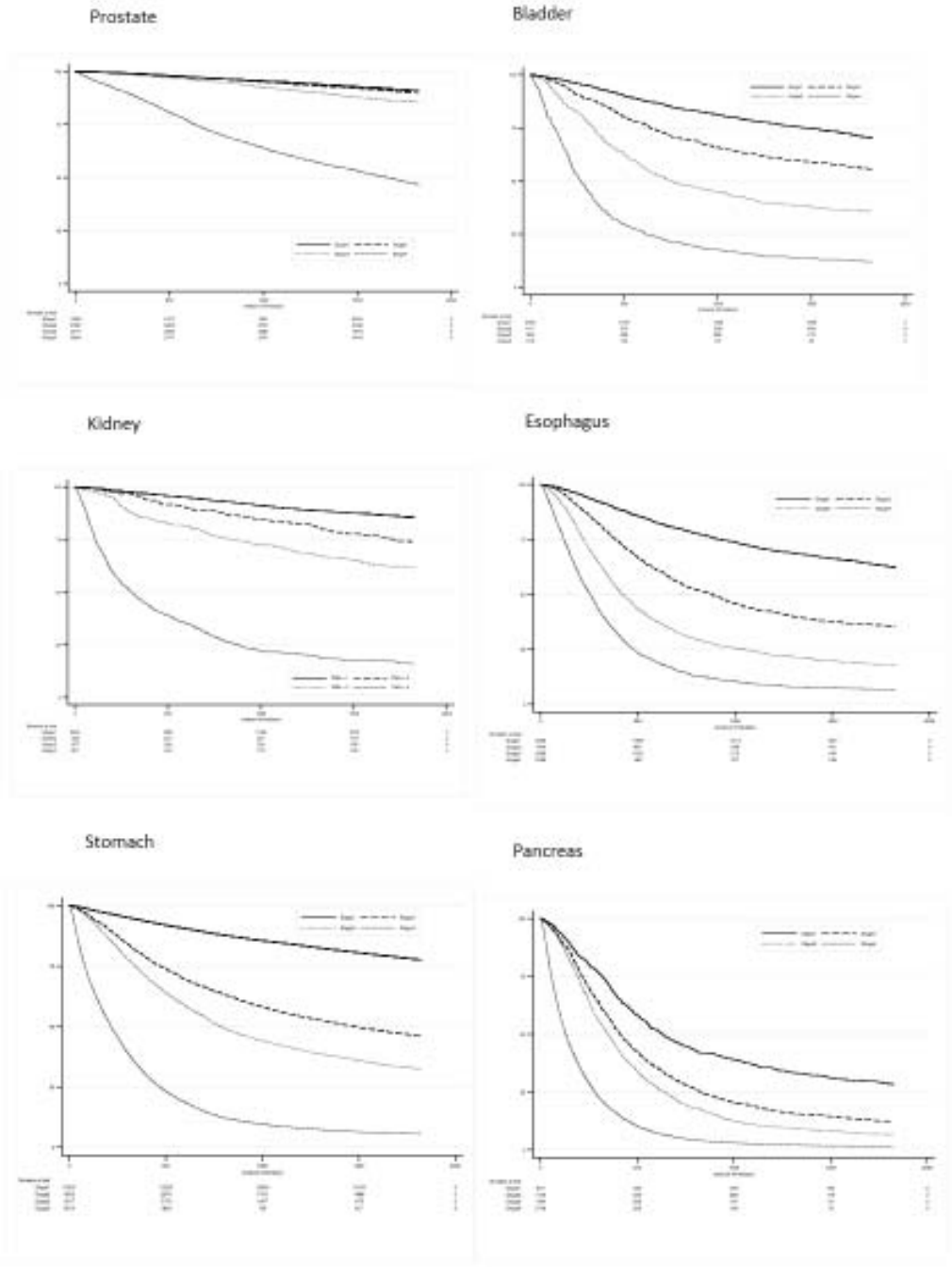

図1　神奈川県地域癌登録における癌のStage別5年生存率

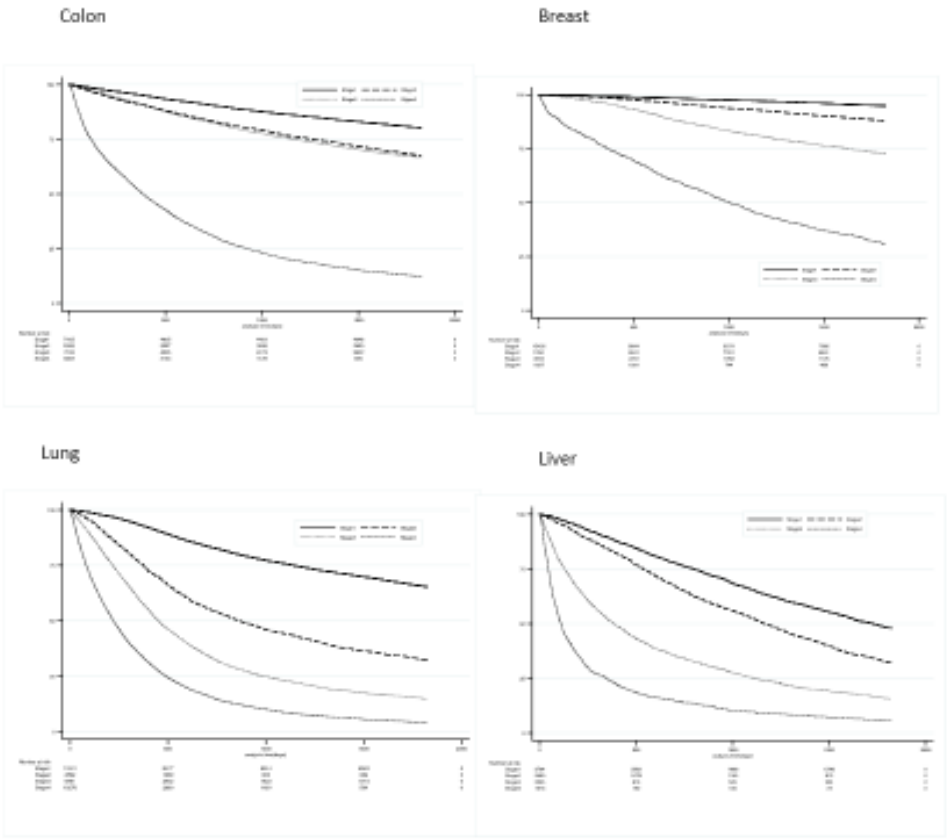

図1　神奈川県地域癌登録における癌のStage別5年生存率　（続き）

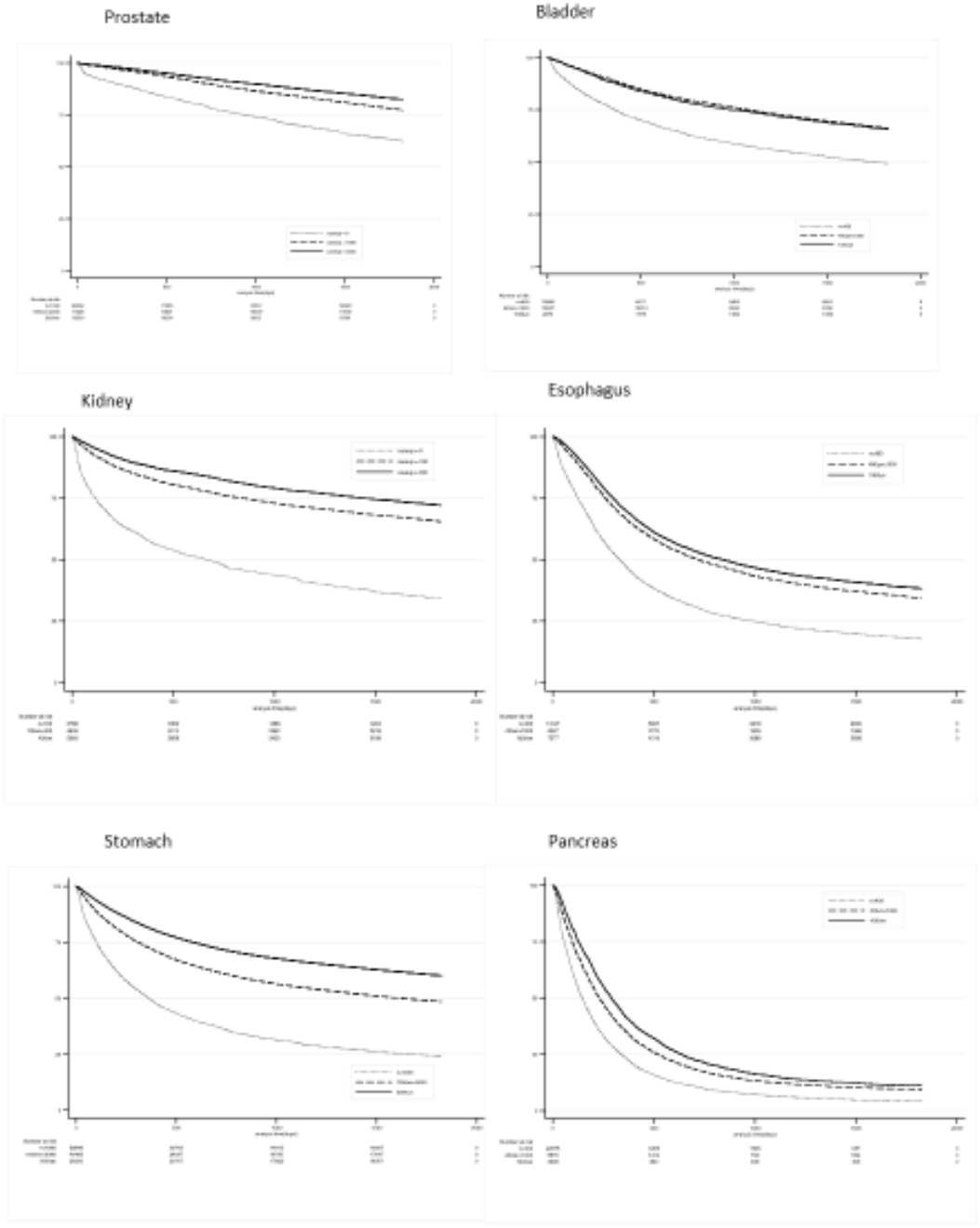

図2　神奈川県地域癌登録における癌の登録施設規模ごとの5年生存率

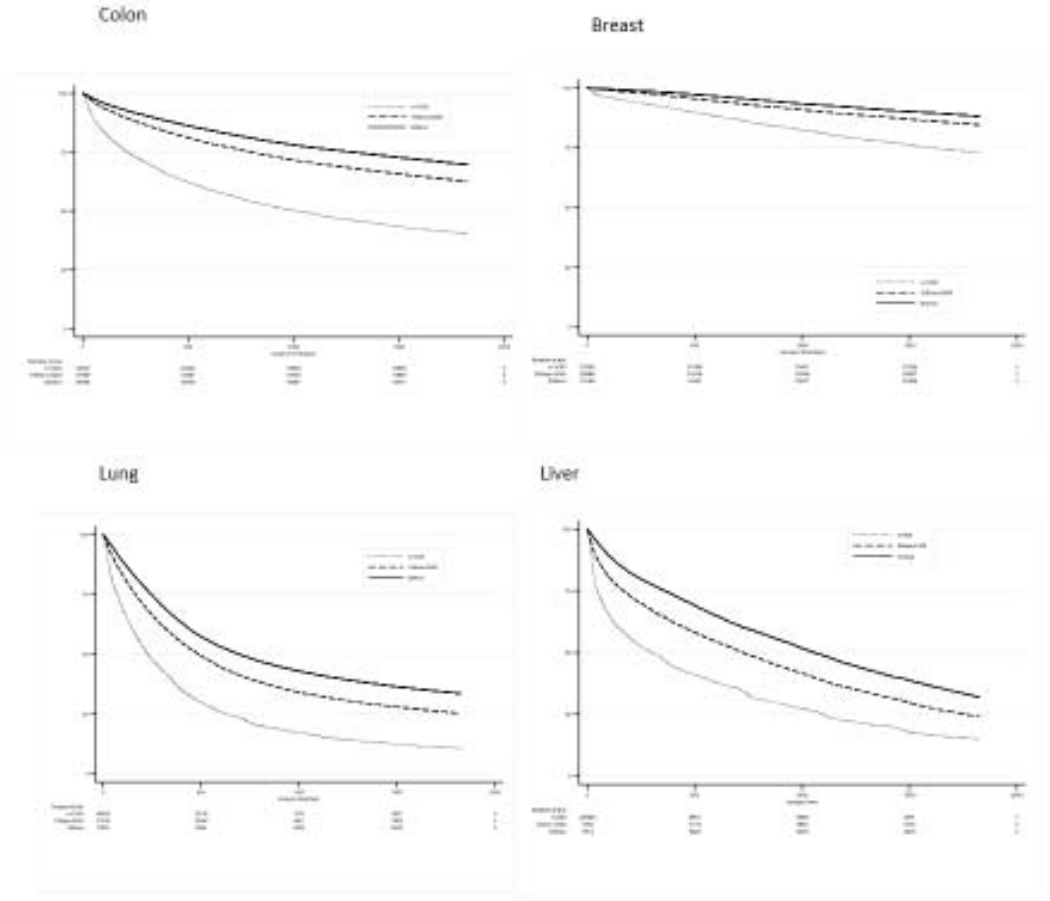

図2　神奈川県地域癌登録における癌の登録施設規模ごとの5年生存率　（続き）

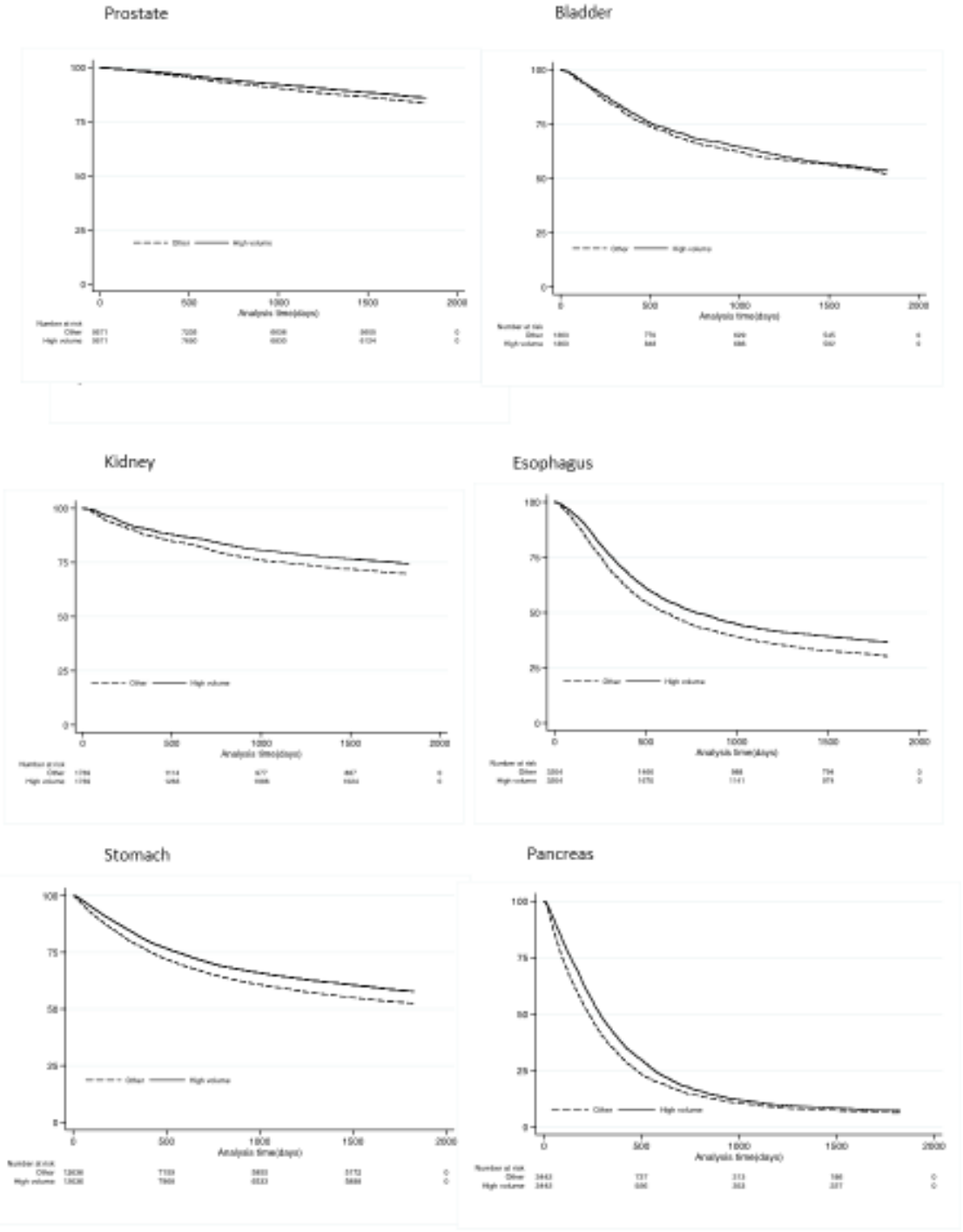

図3　Propensity score matching後の5年生存率

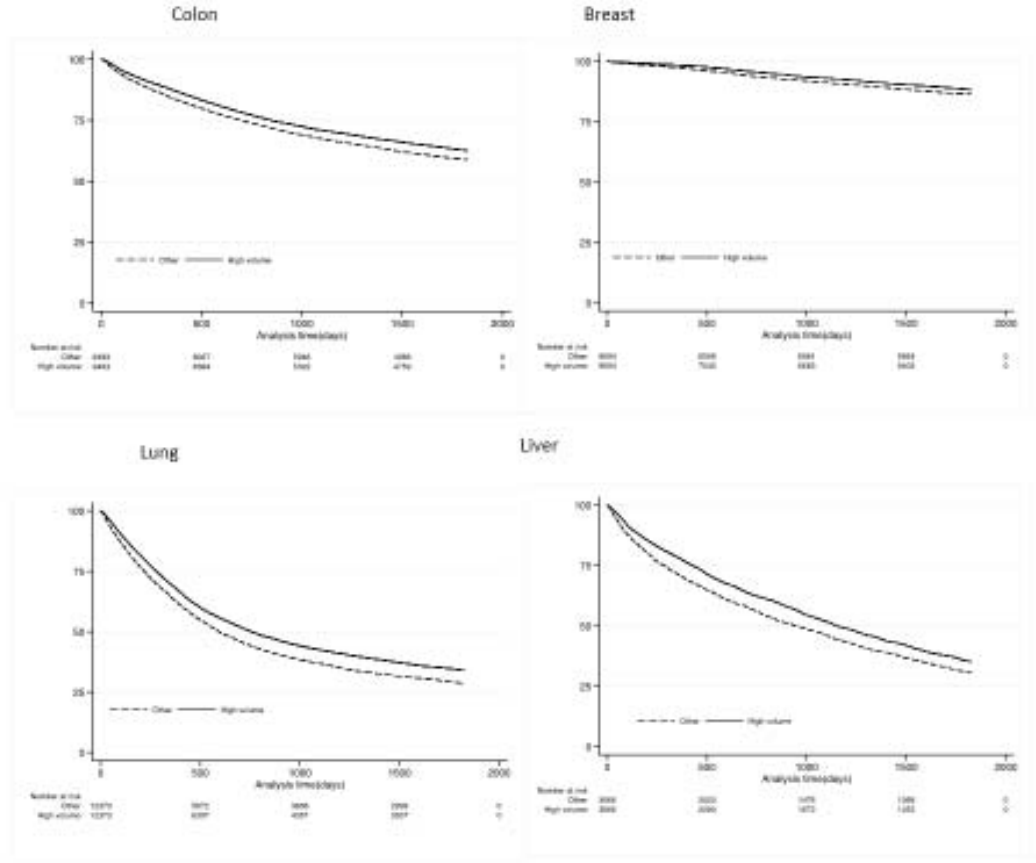

図3　Propensity score matching後の5年生存率 （続き）

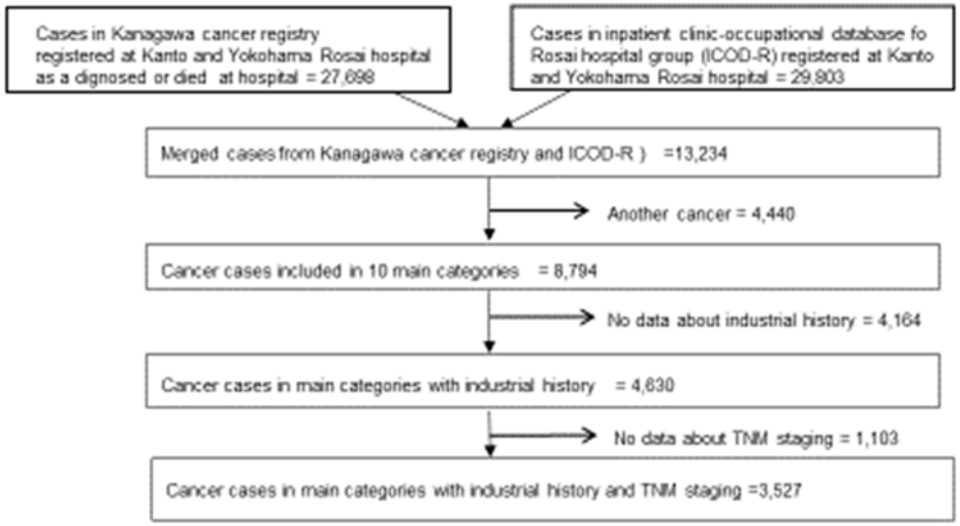

図4　神奈川県地域癌登録と労災病院病職歴データーベース突合の
フローチャート

15

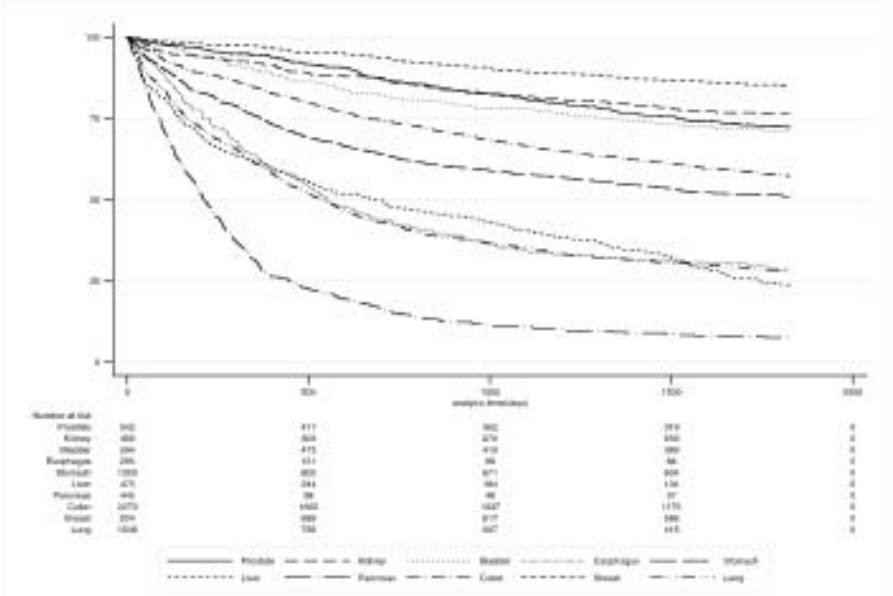

図5　突合全症例の各癌5年生存率

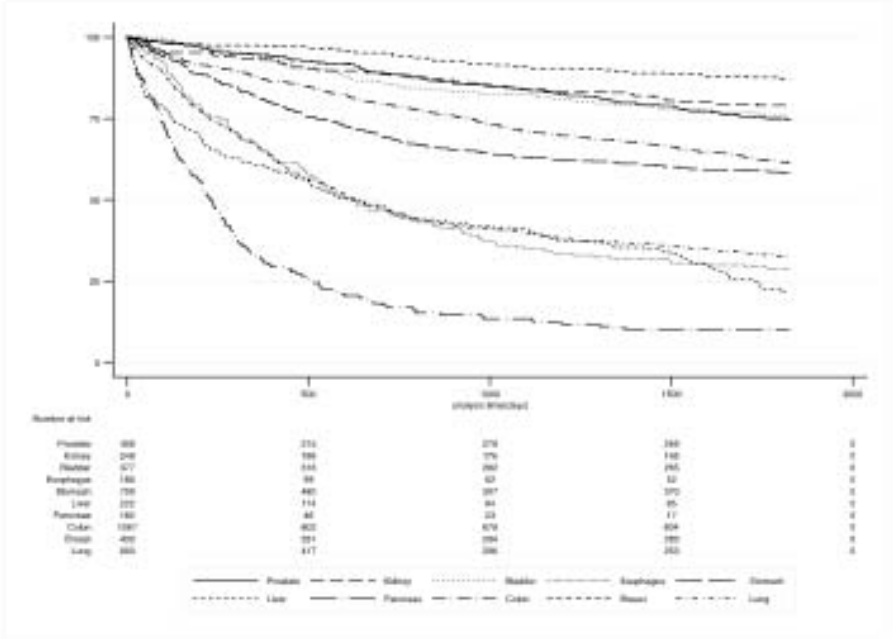

図6　職歴を有する突合症例の各癌5年生存率

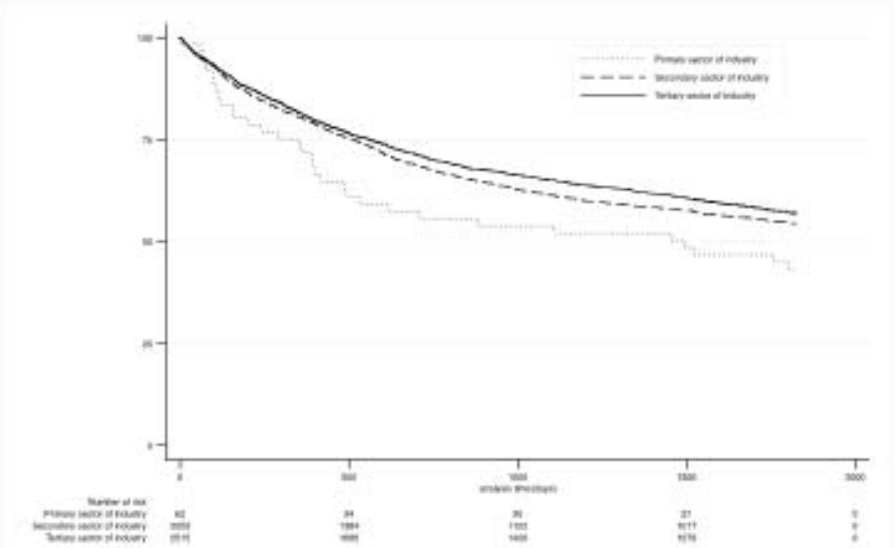

図7　産業群ごとの5年生存率（癌全体）

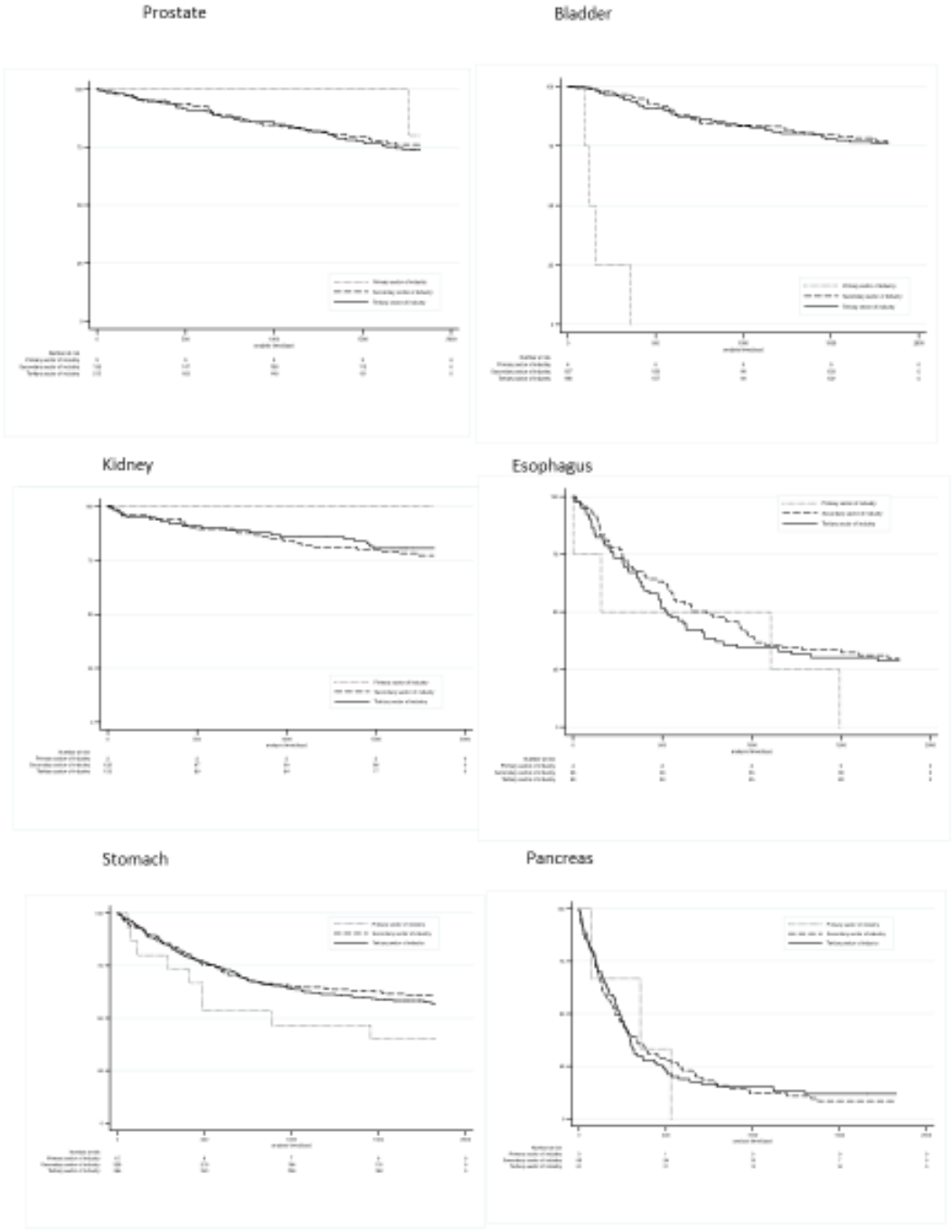

図8　産業群ごとの各癌5年生存率

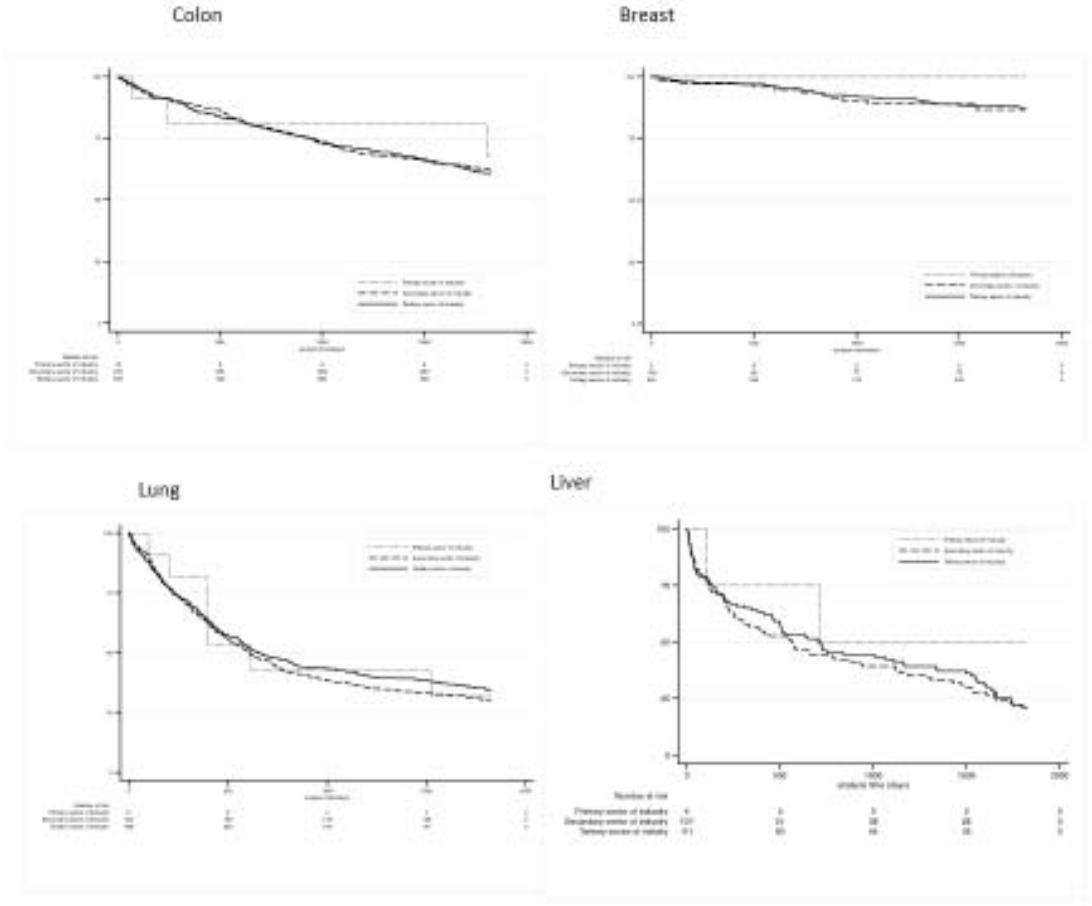

図8　産業群ごとの各癌5年生存率 （続き）

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, Kato S, Kim Y, Takeuchi T, Sato Y, Kobayashi Y, Kawachi I	Occupational Class and Risk of Cardiovascular Disease Incidence in Japan: Nationwide, Multicenter, Hospital-Based Case-Control Study	Journal of American Heart Association	8: e011350	DOI:10.1161/JAHA.118.011350	2019
Kaneko R, Zaitsu M, Sato Y, Kobayashi Y	Risk of cancer and longest‐held occupations in Japanese workers: a multicenter hospital‐based case‐control study	Cancer Medicine	8: 6139-6150	doi: 10.1002/cam4.2499	2019
Zaitsu M, Toyokawa S, Takeuchi T, Kobayashi Y, Kawachi I	Sex-specific analysis of renal cell carcinoma histology and survival in Japan: a population-based study 2004 to 2016	Health Science Reports	e142	doi:10.1002/hsr2.142	2019
Zaitsu M, Takeuchi T, Kobayashi Y, Kawachi I	Light to moderate amount of lifetime alcohol consumption and risk of cancer in Japan	Cancer	126(5): 1031-1040	doi:10.1002/cncr.32590	2020
Zaitsu M, Lee HE, Lee S, Takeuchi T, Kobayashi Y, Kawachi I	Occupational disparities in bladder cancer survival: a population‐based cancer registry study in Japan	Cancer Medicine	9: 894-901	doi: 10.1002/cam4.2768	2020

IV. 研究成果の刊行物・別刷

ORIGINAL RESEARCH

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

Masayoshi Zaitsu, MD, PhD; Soichiro Kato, MD; Yongjoo Kim, ScD, MPH; Takumi Takeuchi, MD, PhD; Yuzuru Sato, MD, PhD; Yasuki Kobayashi, MD, PhD; Ichiro Kawachi, MD, PhD

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

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

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

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

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

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

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Clinical Perspective

What Is New?

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

What Are the Clinical Implications?

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

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

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

Methods

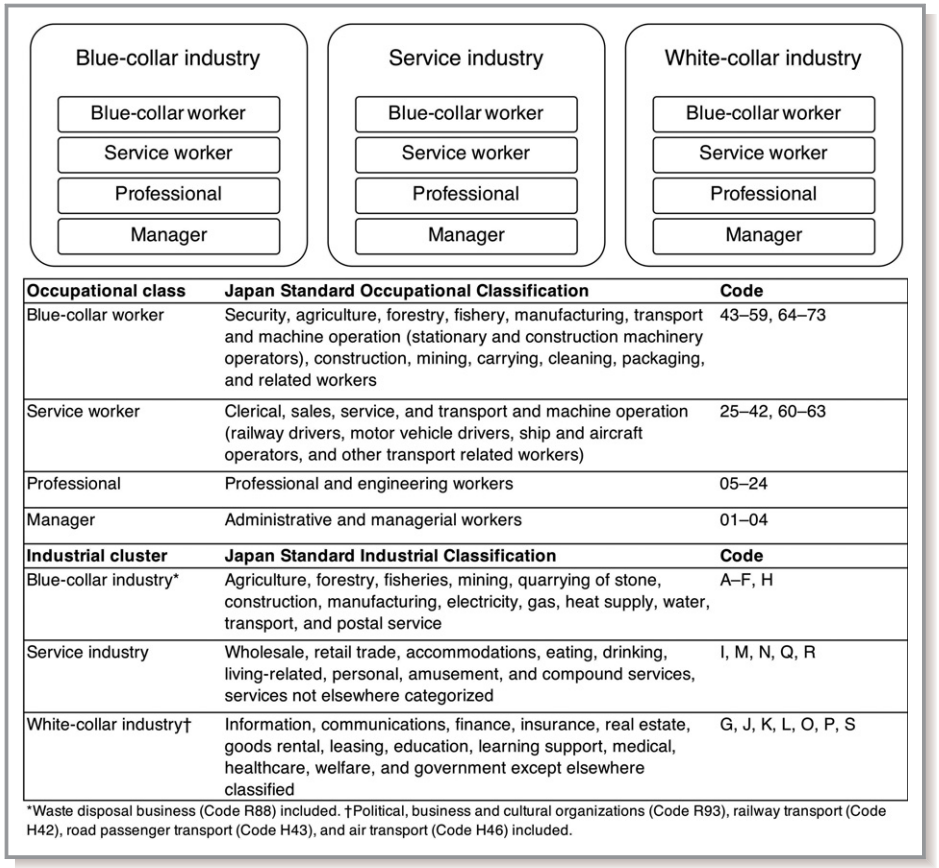
Study Setting

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

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

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

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



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

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

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

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

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

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

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

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

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

Table 3. Background Characteristics Between Cases and Controls

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

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

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

Cases and Controls

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

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

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

Longest-Held Occupational Class Cross-Classified by Industry Sector

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

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

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

Continued

Table 4. Continued

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

Continued

Table 4. Continued

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

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

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

Covariates

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

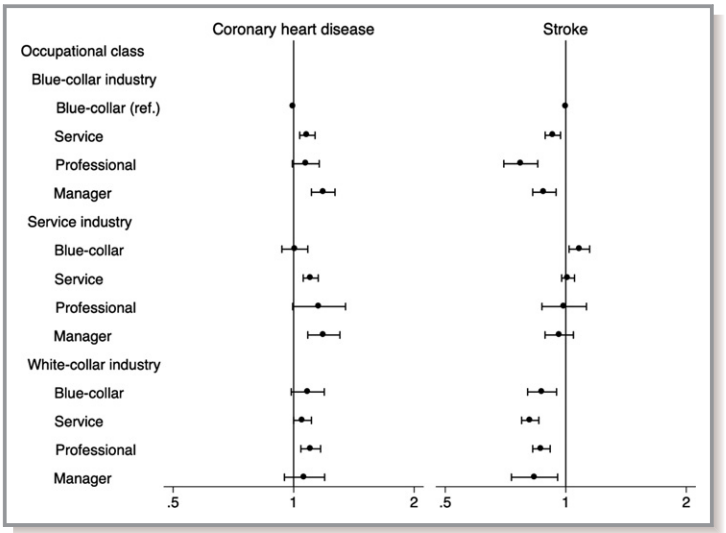


Figure 2. Risk for coronary heart disease and stroke incidence associated with occupational class. The odds ratio (dot) and 95% CI (bar) were estimated by conditional logistic regression with multiple imputation, matched for age, admission date, and admitting hospital, additionally adjusted for smoking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

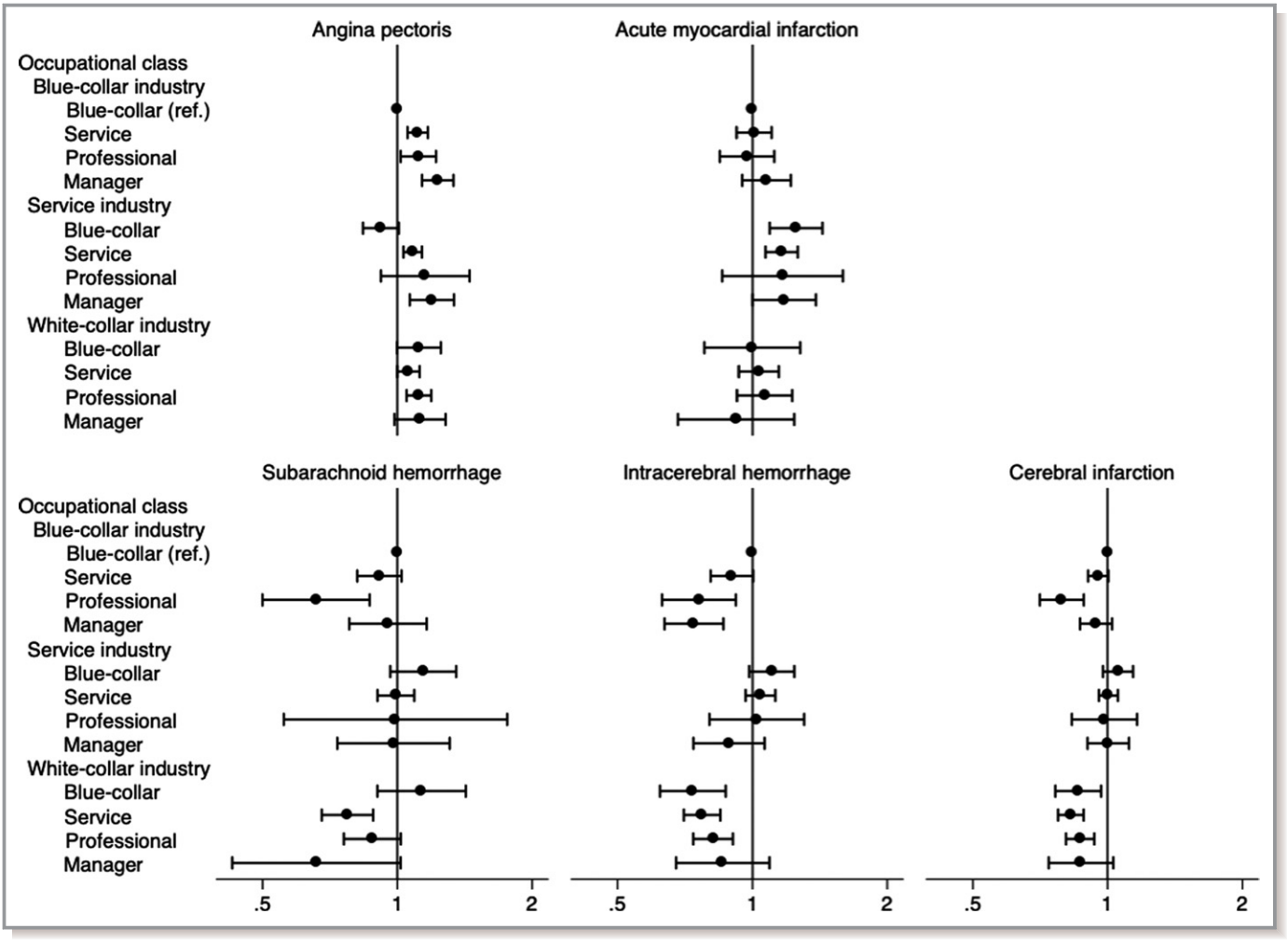


Figure 3. Odds ratios associated with occupational class for incidence of angina pectoris, acute myocardial infarction, subarachnoid hemorrhage, intracerebral hemorrhage, and cerebral infarction. The odds ratio (dot) and 95% CI (bar) were estimated by conditional logistic regression with multiple imputation,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

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

Statistical Analysis

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

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

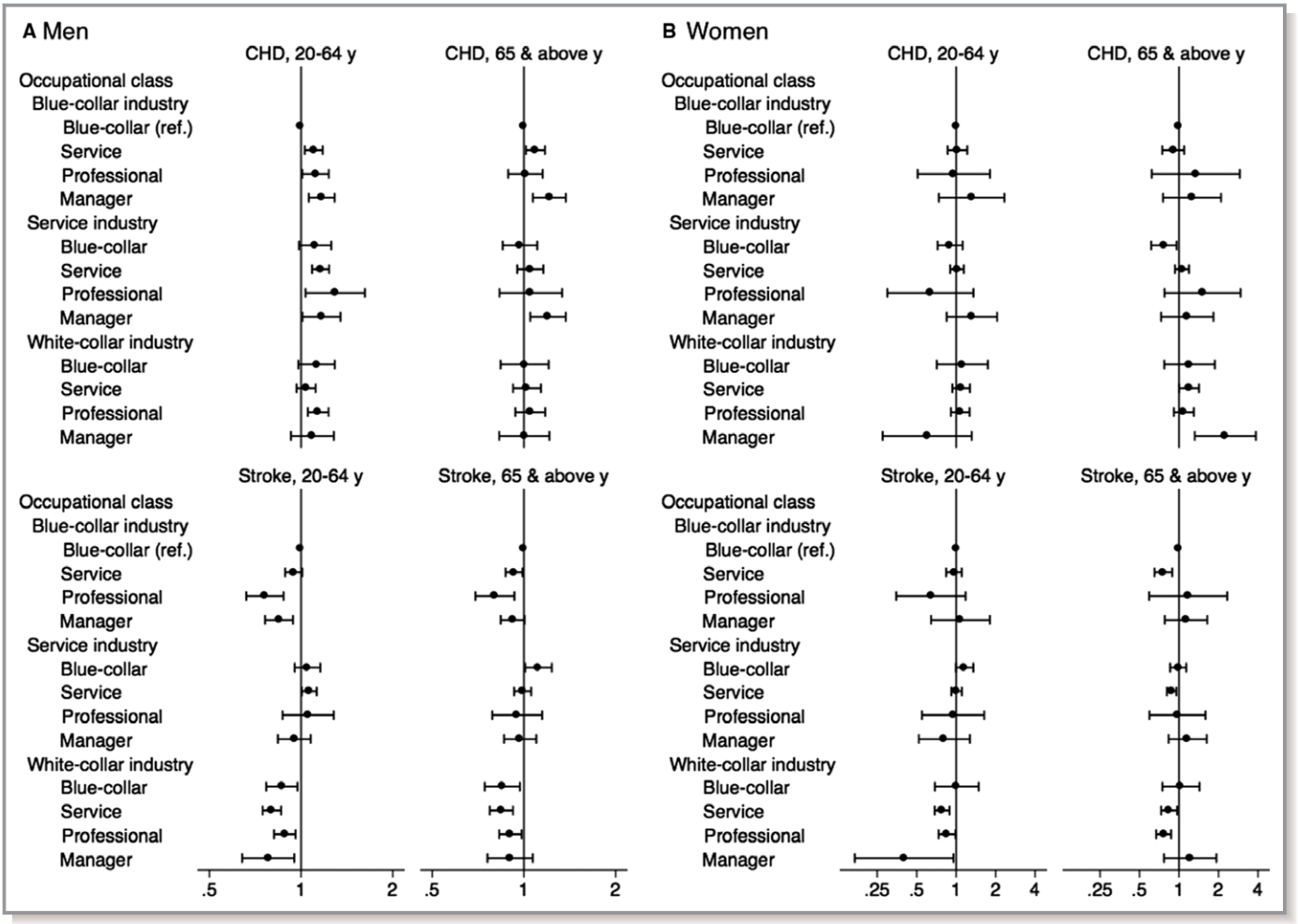


Figure 4. Occupational class gradients stratified by sex and age. The odds ratio (dot) and 95% CI (bar) were estimated by conditional logistic regression with multiple imputation, matched for age, admission date, and admitting hospital, additionally adjusted for smoking and alcohol consumption. The numbers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

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

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

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

Results

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

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

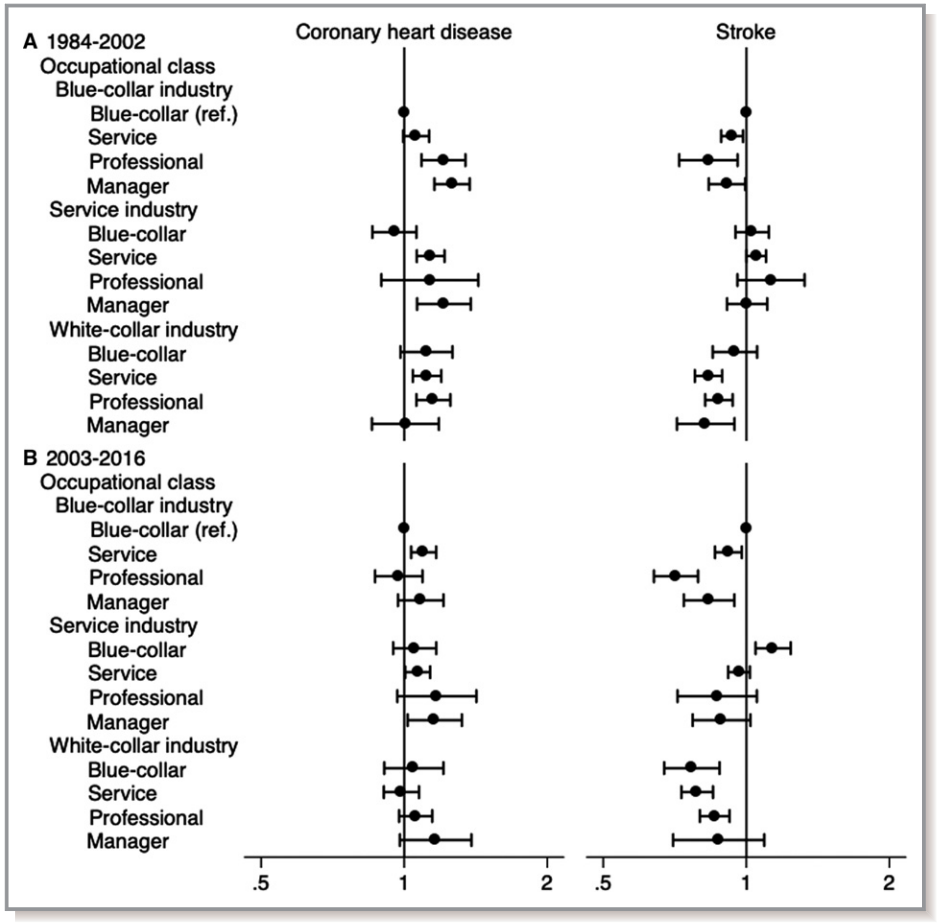


Figure 5. Occupational class gradients stratified by admission period. The odds ratio (dot) and 95% CI (bar) were estimated by conditional logistic regression with multiple imputation, matched for age, admission date, and admitting hospital, additionally adjusted for smoking and alcohol consumption.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

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

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

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

Discussion

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

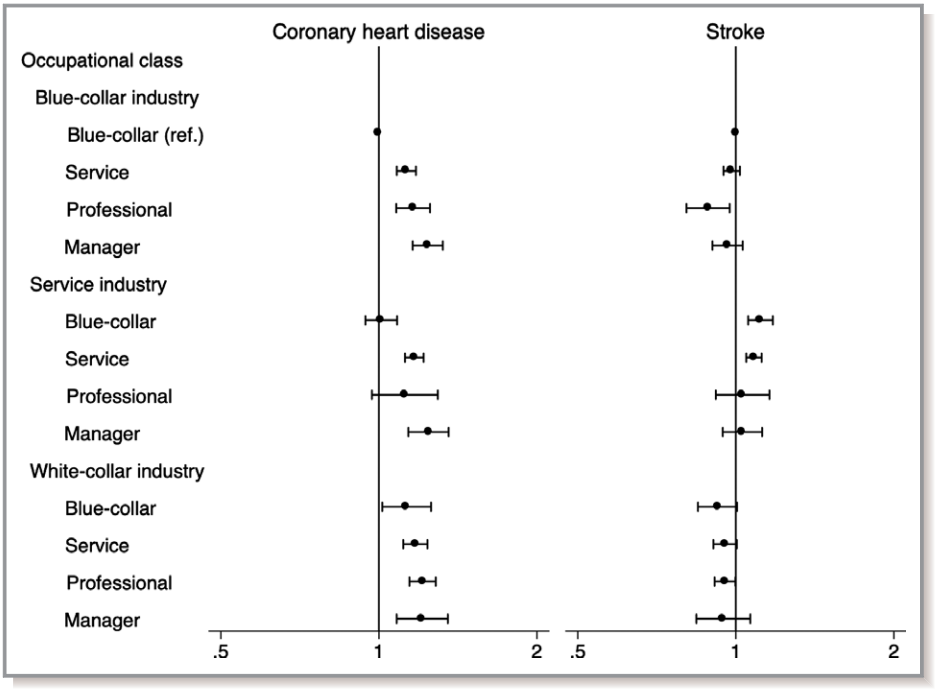


Figure 6. Odds ratio in each occupational class for coronary heart disease and stroke incidence estimated with alternative control groups. The odds ratio (dot) and 95% CI (bar) were estimated by conditional logistic regression with multiple imputation, matched for age, admission date, and admitting hospital,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

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

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

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

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

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

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

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

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

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

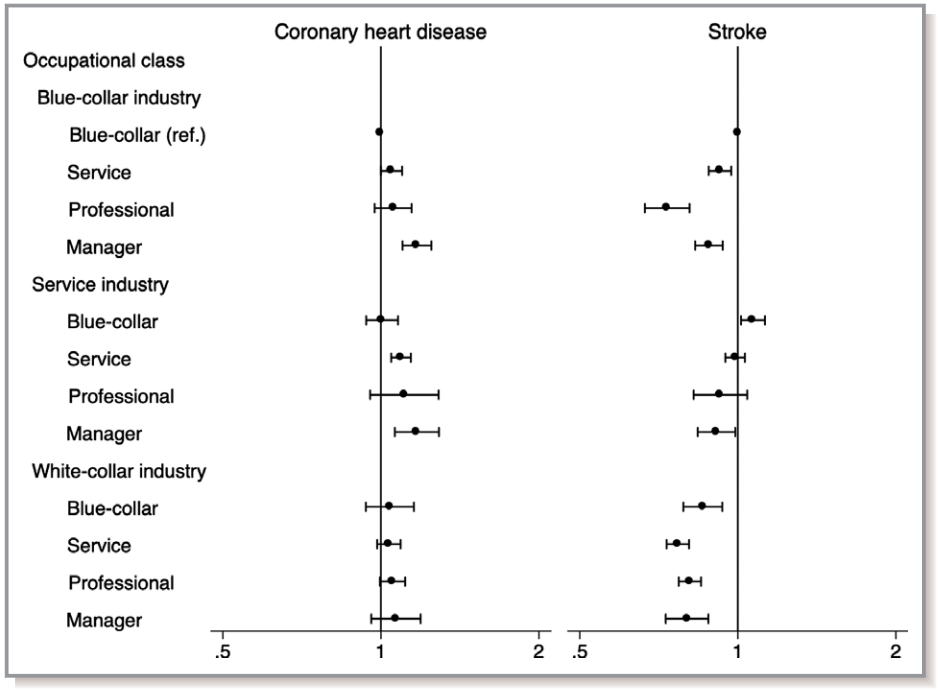


Figure 7. Risks of coronary heart disease and stroke incidence associated with most recent occupational class. The odds ratio (dot) and 95% CI (bar) were estimated by conditional logistic regression with multiple imputation, matched for age, admission date, and admitting hospital, additionally adjusted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

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

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

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

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

Conclusion

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

Author Contributions

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

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Disclosures

None.

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ORIGINAL RESEARCH

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

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Abstract

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

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

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

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

KEYWORDS
cancer, occupational activity, risk

1 | INTRODUCTION

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

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

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

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

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

1.1 | Subjects

1.1.1 | Inpatient Clinico-Occupational Database of Rosai Hospital Group

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

2 | METHODS

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

2.1 | Case and control datasets

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

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

2.2 | Occupation categories and occupational physical activity

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

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

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

2.3 | Statistical analysis

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

3 | RESULTS

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

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

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

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

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

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

4 | DISCUSSION

4.1 | Change of occupational risk in a historical transition

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

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

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

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

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

SD, standard deviation

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

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

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

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

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

[†]IQR:Interquartile range.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

4.2 | Agriculture

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

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

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

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

4.3 | High occupational physical activity and a paradox

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

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

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

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

4.4 | Strengths and limitations

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

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

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

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

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

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

5 | CONCLUSION

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

CONFLICTS OF INTEREST

None.

AUTHOR CONTRIBUTIONS

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

DATA AVAILABILITY STATEMENT

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

INFORMED CONSENT

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

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RESEARCH ARTICLE

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

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Abstract

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

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

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

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

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

1 | INTRODUCTION

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

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

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

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

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

2 | MATERIALS AND METHODS

2.1 | Data setting and study subjects

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

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

2.2 | Histological subtype and 5-year overall survival

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

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

2.3 | Covariates

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

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

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

Abbreviation: SES, socioeconomic status.

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

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

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

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

[e]Missing data are included.

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

2.4 | Statistical analysis

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

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

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

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

3 | RESULTS

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

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

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

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

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

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

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

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

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

4 | DISCUSSION

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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CONFLICT OF INTEREST

The authors declare no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

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

TRANSPARENCY STATEMENT

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

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

DATA AVAILABILITY STATEMENT

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

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Original Article

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

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

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

INTRODUCTION

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

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

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

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

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

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

MATERIALS AND METHODS

Study Setting

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

Cases and Controls

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

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

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

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

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

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

Total Amount of Lifetime Alcohol Consumption and Other Covariates

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

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

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

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

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

Statistical Analysis

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

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

RESULTS

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

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

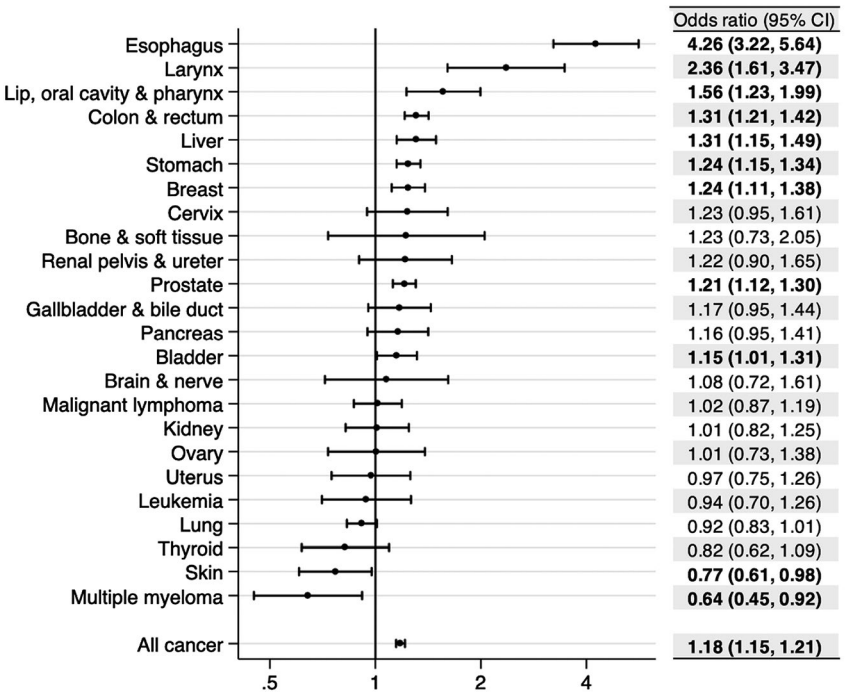

Figure 1. Overall and specific cancer incidence risk associated with ever drinkers. Odds ratios (dots) and 95% CIs (lines) were estimated with 63,232 cases and 63,232 controls by conditional logistic regression matched for sex, age, admission date, and hospital. Smoking history, occupational class, and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

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

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

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

DISCUSSION

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

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

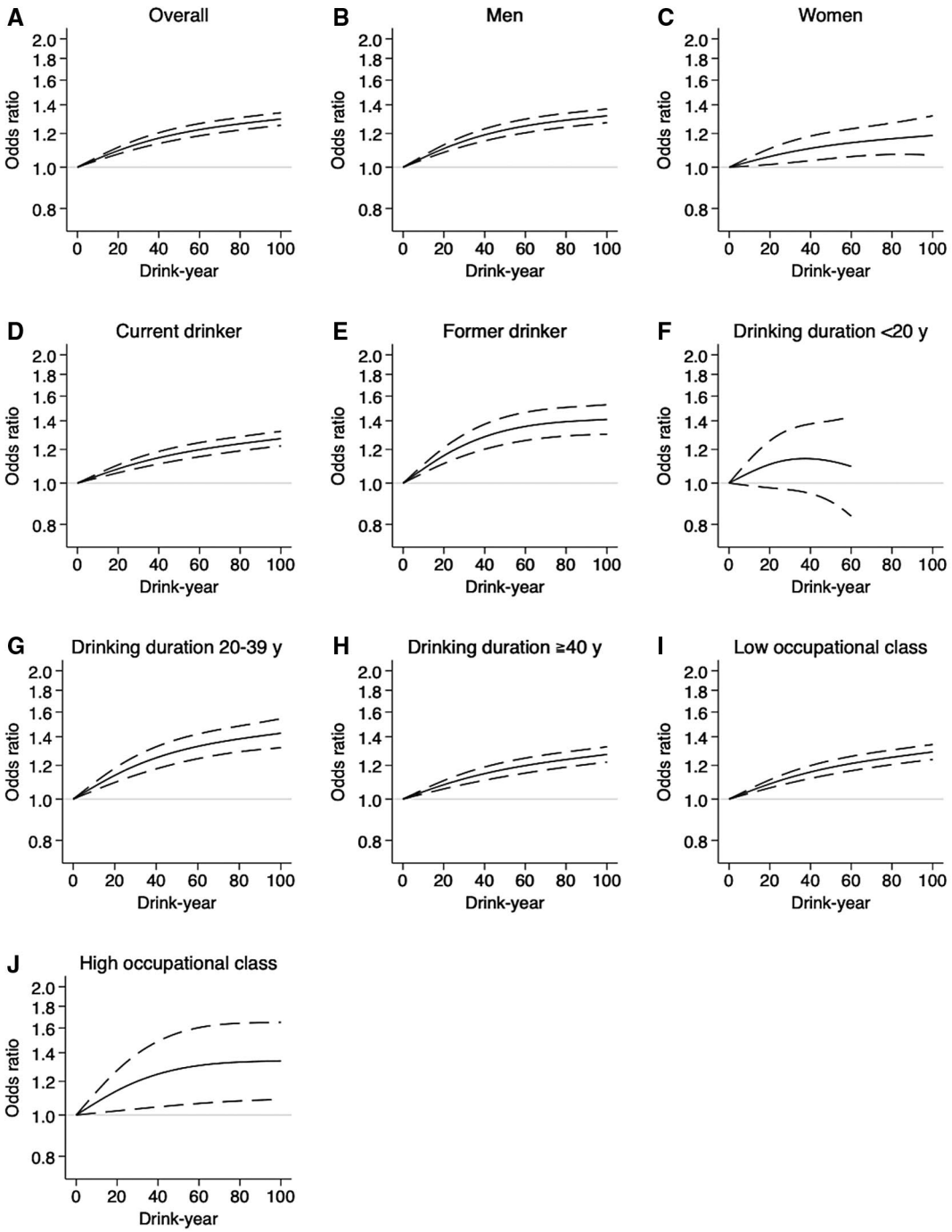

Figure 2. Cubic spline curves for overall cancer risk against the total amount of lifetime alcohol consumption. Odds ratios (solid lines) and 95% confidence intervals (dashed lines) were estimated by conditional logistic regression matched for sex, age, admission date, and hospital. Smoking history and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

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

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

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

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

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

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

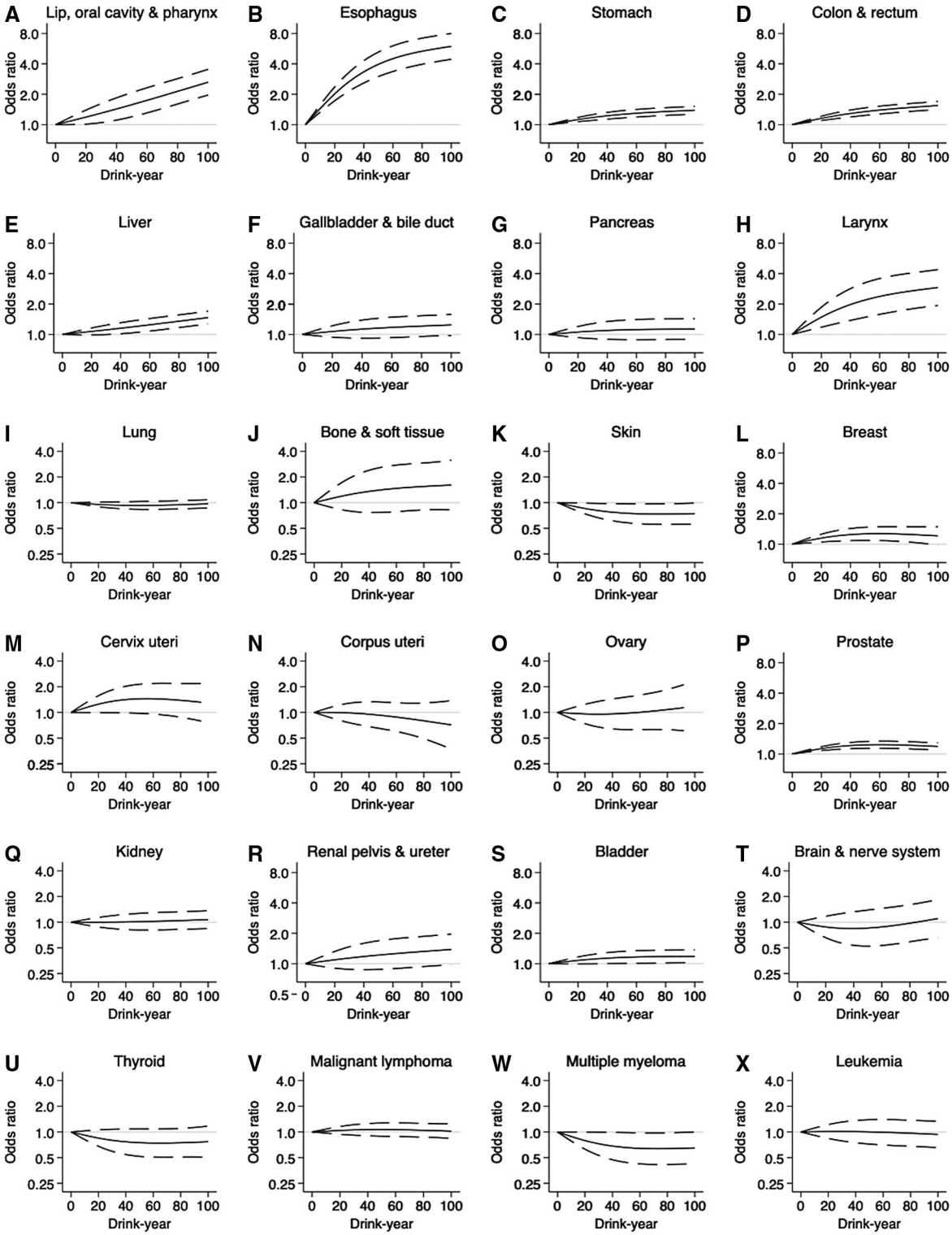

Figure 3. Cubic spline curves for specific cancer risks against continuous total amount of lifetime alcohol consumption. ORs (solid line) and 95% CIs (dashed line) were estimated by conditional logistic regression, mutually adjusted for smoking history, occupational class, and comorbidities. The numbers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

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

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

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

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CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

AUTHOR CONTRIBUTIONS

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

DATA AVAILABILITY STATEMENT

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

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ORIGINAL RESEARCH

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

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Abstract

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

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

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

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

KEYWORDS

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

1 | INTRODUCTION

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

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

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

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

2 | MATERIALS AND METHODS

2.1 | Data setting

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

2.2 | Main outcome and study subjects

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

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

2.3 | Occupational class

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

2.4 | Covariates

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

2.5 | Statistical analysis

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

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

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

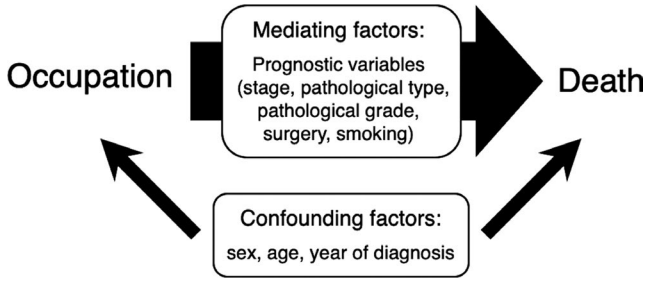

FIGURE 1 Confounding and mediating variables in the analytic model

3 | RESULTS

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

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

FIGURE 2 Overall survival curves by longest-held occupations

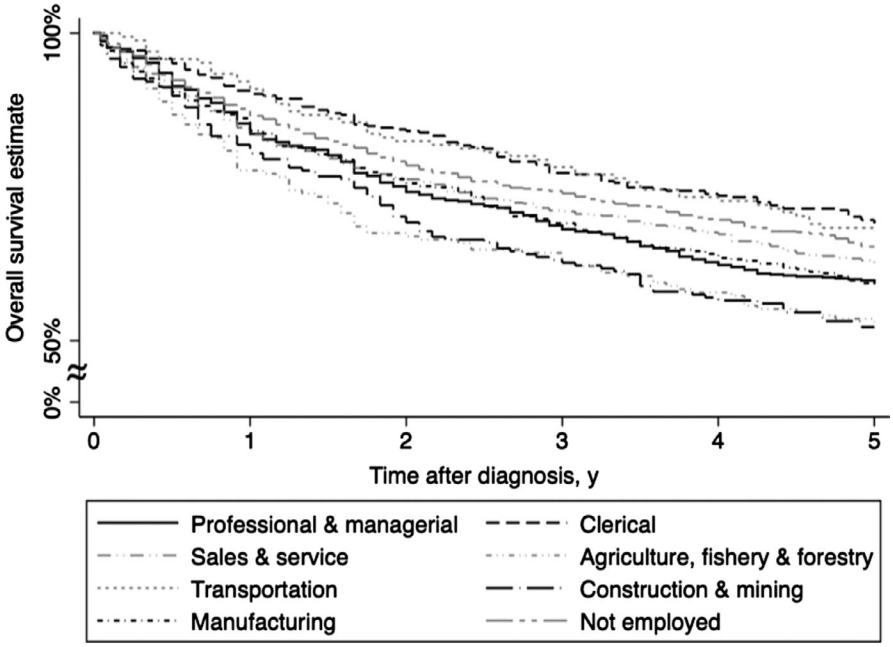

TABLE 1 Characteristics of bladder cancer patients who completed occupational information in Kanagawa Cancer Registry

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

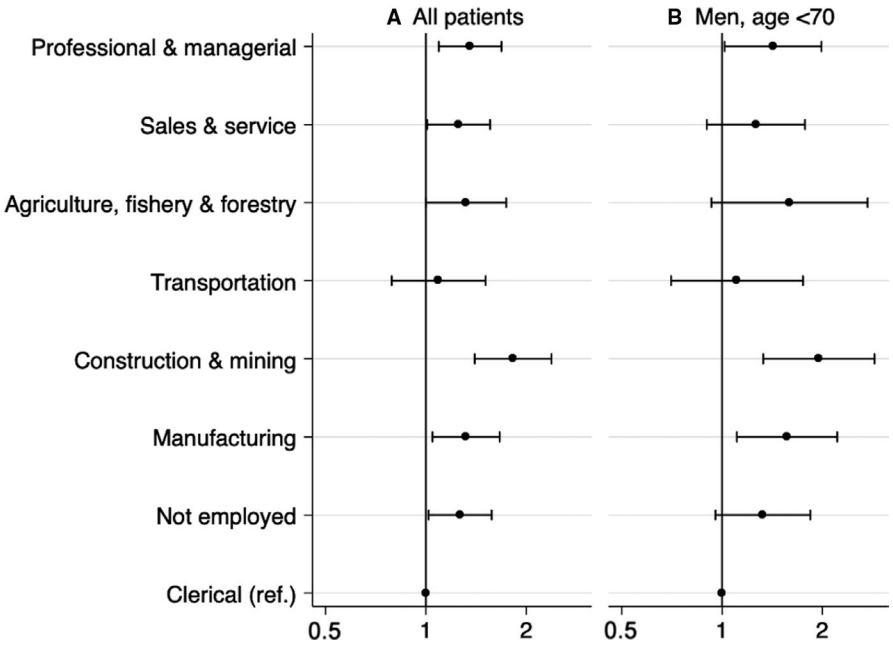

FIGURE 3 Occupational disparities in bladder cancer survival estimated with Cox proportional hazard model. Hazard ratios (circle) and 95% confidence intervals (line) were adjusted for sex, age, and year of diagnosis among (A) all study patients (n = 3593) and (B) male patients aged < 70 (n = 1900)

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

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

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

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

4 | DISCUSSION

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

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

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

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

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

*$P < .05$.

**$P < .01$.

***$P < .001$.

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

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

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

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

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

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

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

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

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

CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

AUTHOR CONTRIBUTIONS

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

DATA AVAILABILITY STATEMENT

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

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