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、まず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。まず、腎細胞がんと職業の関連に焦点をあて、詳細な分析を行った。さらに、研究分担者や研究協力者の協力を得て、幅広い業種・職種を対象にして種々のがん種の発生状況や予後について網羅的、探索的な検討を行った。また、有害物質曝露と関連がしばしば指摘される尿路系腫瘍について、病因論検討を行った。

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 600 万件の入院患者病職歴調査データベースである。同データベースの職業歴は、日本標準職業分類 JSOC および日本標準産業分類 JSIC を用いて、現職から過去 3 つまでの職業分類がコーディングされている。腎細胞がんの分析では、最長の職業を用いて対象者を 4 つの基本的な職業地位、「ブルーカラー職」、「サービス職」、「専門職」、「管理職」に分類した。産業についても 3 種類に分類した。解析対象者は 20 歳以上、1984 年 4 月から 2016 年 3 月までの入院患者 71,734 名で、腎細胞がん 3,316 名（上部尿路上皮がん、およびがん既往歴があるものは除く）と対照群として設定した 168,418 名の良性疾患患者が含まれる。解析の結果、男性において、ブルーカラー産業のブルーカラー職従事者と比べると、全ての産業で職業地位の高い人（専門職や管理職）で腎細胞がんのリスクが高かった。さらに詳細な解析から、高血圧、糖尿病、肥満等のストレス関連因子を通じて、職業地位の高い人の腎細胞がんのリスクが上昇する経路が示唆された。また、同データベースを用いた研究分担者らの研究からは、第一次産業でいくつかのがん種に対するオッズ比が他の業種よりやや低く、逆に第三次産業でやや高い傾向が示された。地域がん登録データベースを用いた解析からは、胆管がんの予後の改善と予後に関連する要因を明らかにした。本研究の成果として、既存の大規模医療データを職業とがんの関連についてのサーベイランス手法に利活用できる可能性が示された。

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A. 研究目的

近年、わが国では、化学工業製造従事者の膀胱がんや、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、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。本報告では、主に腎細胞がんに焦点をあてた詳細な解析結果を報告する。

腎細胞がんは、日本では罹患率が 2%程度ではあるが、近年は罹患率が増加傾向にある。欧米で知られている腎細胞がんのハイリスク職業（化学工業生産工程従事者、機械整備・修理従事者、ドライクリーニング、理容師・美容師）については、予備的分析ではリスクは上昇していなかった。一方で、欧米では、腎細胞がんのリスクファクターとして喫煙、高血圧等が知られており、これらは職業ストレスと関連していることが知られている。日本では職業地位の高い人（専門職や管理職従事者）で、近年自殺率が上昇していることから（Suzuki 2013, Tanaka 2017）、高い職業地位と職業ストレスの関連が示唆されており、新たな職業的リスクの可能性もある。そこで、まず、業種・職種を職業地位として意味のあるグループに網羅的に分類し、各産業別の各職業地位における腎細胞がんのリスクの網羅的に解析することを目的とした。さらには、これらの職業地位と腎細胞がんの関連が、ストレス関連因子（喫煙や高血圧等）を調整しても持続するかどうか検討した。

また、研究分担者や研究協力者の協力を得て、幅広い業種・職種を対象にして種々のがん種の罹患状況や予後について網羅的、探索的な検討を行った。さらに、有害物質曝露と関連がしばしば指摘される尿路系腫瘍について、病因論検討を合わせて行った。これらの研究結果については、分担研究報告において扱う。

B. 研究方法

<u>データセッティング</u>

独立行政法人労働者健康安全機構が保有する約 600 万件の入院患者病職歴調査データを用いて hospital-based case-control study を実施した。入院患者病職歴調査データとは、全国 34 箇所の労災病院に入院した全入院患者の病歴および職業歴を抽出したデータであり、独立行政法人労働者健康安全機構が中央情報センターとして、1984 年からデータベース化を行っている。このデータベースには、各患者の性・年齢等の基本的背景、退院時の主病名、並存疾患名の他に、喫煙、飲酒の生活習慣行動が保有されている。また、2002 年からは病理診断、2005 年からは健康診断で指摘されてい

る生活習慣病（高血圧、糖尿病、肥満等）の情報も保有されている。職業歴については、日本標準職業分類 JSOC および日本標準産業分類 JSIC を用いて、現職から過去 3 つまでの職業分類がコーディングされている。これらの職業分類は、世界標準職業分類および世界標準産業分類と対応している。患者からのデータ取得およびデータベースへのデータ登録は訓練を受けた専門の臨床情報士、看護師等が実施し、患者からインフォームドコンセントを取得している。詳細については先行研究で報告されている（Zaitsu 2016, Zaitsu 2017）。研究者らと独立行政法人労働者健康安全機構との取り決めに基づき、匿名化されたデータセットを取得した。

症例 case と対照 control

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

職業分類

取得した入院患者病職歴調査データでは、現職から過去 3 つまでの職業が、JSOC および JSIC の 3 桁コードで分類されていたため、最長の職業を用いて各患者を層別化した。抽出された最長職業の種類は莫大な数となるため、4 つの基本的な職業地位、「ブルーカラー職」、「サービス職」、「専門職」、「管理職」に分類した（Tanaka 2017）。また、さらにこの職業地位を 3 つの産業別、「ブルーカラー」、「サービス」、「ホワイトカラー」に分けた（図 1）(Jackson 2013)。主婦、学生、無職等の雇用されていない者は解析から除外した。また、女性のホワイトカラー産業の「管理職」については、人数が非常に少なく、腎細胞がんの case を認めなかったため、解析から除外した。また、欧米で知られている腎細胞がんのハイリスク職業（化学工業生産工程従事者、機械整備・修理従事者、ドライクリーニング、理容師・美容師）については、解析の過程でリスク増加を認めなかったため、新たにグループ分けは行わなかった。

共変量

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

統計解析

解析対象者のうち 11%は、職業、喫煙、飲酒の情報いずれかが欠損しており、20%は職業、喫煙、飲酒の情報いずれも欠損していた。データ欠損群とデータ完全群では患者背景が統計学的に異なっていたため、データ欠損群を除外して解析することはデータ解釈にバイアスを生じる可能性があった。よって、解析対象者 171,734 名の全データを利用して multiple imputation by chain method（MICE）法による多重補完 multiple imputation を実施し、数学的に欠損値を予測し代入した（Hayati Rezvan 2015, Royston 2009, Zaitsu 2018）。職業（n = 20,359, 12%）、喫煙（n = 23,692, 14%）、飲酒

（n = 48,608, 28%）の欠損値が代入された。Multiple imputation によって作成された 5 個のデータセットを用いた unconditional logistic regression により、ブルーカラー産業のブルーカラー職に対する各職業の腎細胞がんのオッズ比（odds ratio, OR）および 95%信頼区間（95% confidence interval, 95%CI）を算出した。すべての解析は男女別でおこなった。第一に、年齢と入院日（年）を調整した OR（95％CI）を求めた（モデル 1）。次に追加で喫煙を調整した OR（95％CI）を求めた（モデル 2）。さらに飲酒を調整した OR（95％CI）を求めた（モデル 3）。

高血圧、糖尿病、肥満が職業と腎細胞がんの関連にどのように関与するかは、これらのデータが 2005 年以降しか取得可能でなかったため、2005 年以降に入院した 63,704 名（1,544 名の case、62,160 名の control）を対象に、以下の欠損値を多重補完し解析した：職業（n = 6,943, 11%）、喫煙（n = 6,968, 11%）、飲酒（n = 19,198, 30%）、高血圧（n = 8,507, 13%）、糖尿病（n = 8,508, 13%）、肥満（n = 8,508, 13%）。このサブグループ解析では、高血圧の関与をまず評価し（モデル 4)、最終的に高血圧、糖尿病、肥満、年齢、入院日（年）、喫煙、飲酒の全てを調整して、各職業の腎細胞がんの OR（95％CI）を求めた。入院患者を対照群として用いることで選択バイアスが生じる可能性があるため、(1) 全ての良性疾患の対照群（3,316 名の case と 1,298,207 名の control)と、(2)整形外科疾患患者のみの対照群（3,316 名の case と 150,210 名の control)を用いた 2 種類の感度分析を追加した。さらに、完全データ群による complete case analysis（2,496 名の case と 116,139 名の整形外科疾患 control 群)も実施した。統計学的有意水準は両側 5％とし、STATA/MP13.1 （ Stata-Corp LP, College Station, Texas）を使用して統計解析を行った。

（倫理面への配慮）

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

C. 研究結果

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

サブグループ解析においては、男性では、高血圧、糖尿病、肥満がそれぞれ独立した腎細胞がんのリスク因子であった（高血圧 OR＝1.36、95% CI 1.20−1.54、モデル 5)。職業地位の高い人と関連する腎細胞がんのリスクは、高血圧や喫煙等の全ての交絡および中間媒介因子を調整することにより大きく減少したものの、専門職においてはブルーカラー産業（OR＝1.37、95% CI 1.06−1.78）とホワイトカラー産業（OR＝1.26、95% CI 1.00−1.59）では、腎細胞がんのリスクと関連が持続した（モデル 5)。女性については、有意ではないものの、サー

ビス産業で職業地位の高い人と関連する腎細胞がんのリスクの関連の傾向が見られた(モデル 5)。感度分析でも同様のパターンを示した。また、本データベースの職業地位の分布は、日本の一般人口における職業地位の分布と同様であり、最長職業の平均期間は 20 年以上であった。

D. 考察

本研究により、職業地位と腎細胞がんのリスクの関連が初めて示された。すなわち、男性において、職業地位が高い人の方が腎細胞がんのリスクが高いことが示された。また、日本においては、高血圧が腎細胞がんの独立したリスクファクターであることを初めて明らかにし、高血圧、糖尿病、肥満等のストレス関連因子を通じて、職業地位の高い人の腎細胞がんのリスクが上昇する経路が示唆された。これらの結果は職業ストレスと腎細胞がんとの関連の可能性を示唆している。

職業ストレスと腎細胞がんの関連の pathway は、直接作用 direct pathway と間接作用 indirect pathway が挙げられる。直接作用 direct pathway としては、ストレスが、例えば酸化ストレス等を通じて、生物的化学的にキャンサーステムセルを刺激する pathway が考えられる(Hori 2007, Ganesamoni 2012)。今回は、生活習慣因子(高血圧、糖尿病、肥満)が職業地位と腎細胞がんのリスクの関連に大きく寄与していたが、ブルーカラー産業やホワイトカラー産業でも、有意な関連が持続したことから、direct pathway が腎細胞がんのリスクを増加させる可能性が示唆された。一方、間接作用 indirect pathway は、ストレスと関連する職業地位により、腎細胞がんのリスクファクターである生活習慣因子(喫煙や高血圧等)のリスクを介して、結果的に腎細胞がんのリスクが増加する経路である。先行研究では、精神的ストレス、例えば慢性的な職業環境ストレスが、これらの生活習慣因子のリスクを増加させることがわかっている(Cuevas 2017, Trudel-Fitzgerald 2015)。本研究でも、40 pack-year 以上の喫煙者の割合は、管理職従事者の方が非管理職従事者より高く(25%対 11%)、高血圧の有病率も管理職の方が高かった(37%対 27%)。日本社会において、サービス産業では、伝統的にサービス精神、いわゆる「おもてなし」を含めたホスピタリティーが過度に期待されている。よって、サービス産業の管理職従事者等は顧客の期待を満たそうとして、職業ストレスが大きい可能性がある。日本の管理職従事者のストレスの状況は、過労死を含めたワークライフバランスとの関連が示唆されている(Eguchi 2016)。一方、欧米社会においては、イギリスの Whitehall study が示してきたように、job control の低いブルーカラー職従事者で健康アウトカムの悪いことがわかっており、job control が低いと仕事以外の身体活動も低いことが知られている(Bosma 1998, Gimeno 2009)。本研究は、日本で行われた腎細胞がんと職業リスクに関わる最大規模の研究の1つであるが、それでも日本全体で発症した腎細胞がんの 1%未満しか捉えておらず、本研究の一般化可能性については限定的であるといえる。

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

本研究の限界は、第1に、hospital-based case-control 研究の研究デザイン上、選択バイ

アスが生じている可能性がある点である。しかし、コントロール群を変更して解析した感度分析でも得られた結果は同様であった。第2に、欠損値が多く結果の解釈に影響を与える可能性があったが、multiple imputation と complete case analysis のいずれの手法でも結果は同様であった。第3に、職業地位は必ずしも完全なストレスの指標でない。職業地位は不安や鬱などのメンタルヘルスの指標でもあり、身体活動度の指標でもある（Otsuka 2000, Kawakami 2004）。例えば、低身体活動度と腎細胞がんのリスクの関連がわかっており（Moore 2008）、日本の労働者においては、職業地位の高い人ほど、仕事およびレジャータイムでの身体活動度が低いことが報告されている（Takao 2003）。今後は、これらの未測定の媒介因子が、本研究で示された職業地位と腎細胞がんのリスクとどのような関連があるか明らかにしていく必要がある。

E. 結論

大規模な入院患者病職歴調査データを用い、最長の職業歴を用いて解析対象者を層別化することにより、男性労働者における職業地位と腎細胞がんのリスクとの関連を初めて報告した。また、生活習慣について検討したところ、上記の関連は高血圧等の生活習慣因子を介している可能性が示唆された。既存の大規模医療データ等を用いた詳細な解析が、職業とがんとの関連に関わるサーベイランス手法として有用な可能性がある。

F. 健康危険情報

なし

G. 研究発表

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2．学会発表

なし

H. 知的財産権の出願・登録

なし

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

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

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

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

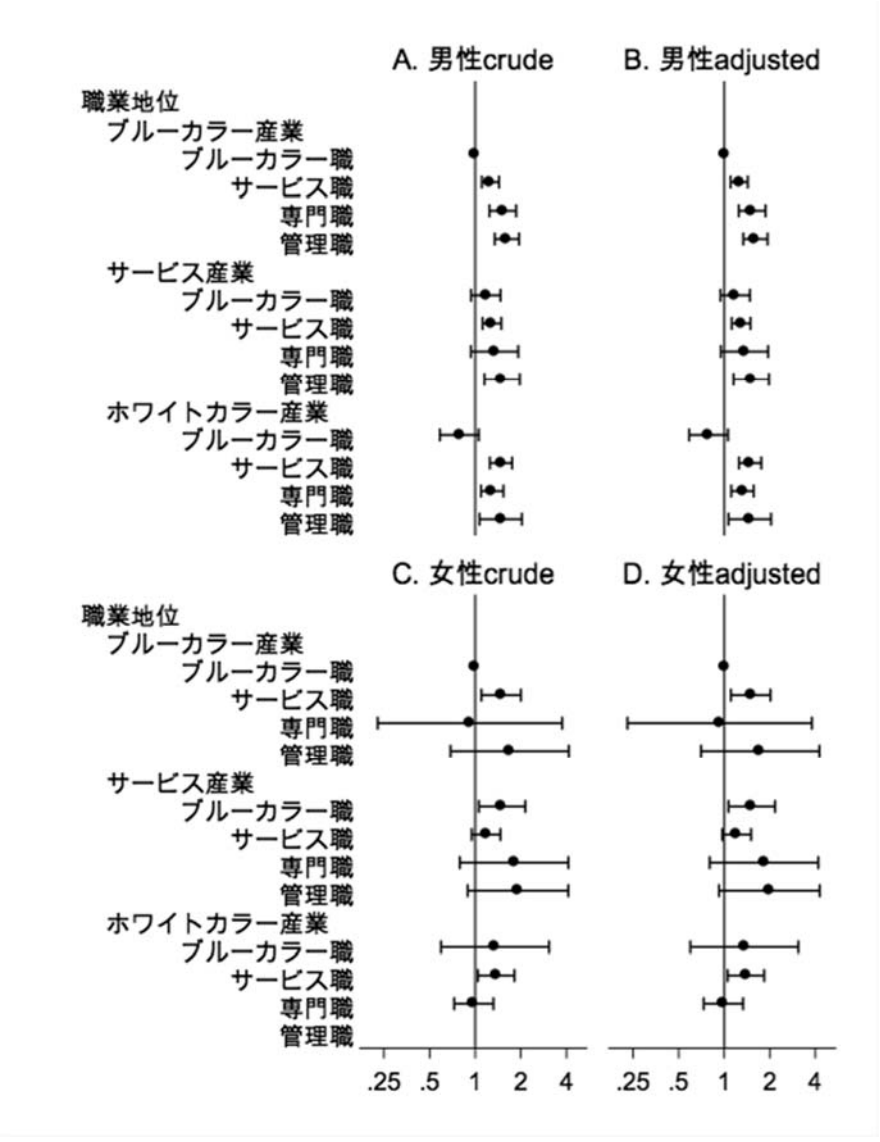

表 1.各職業地位・産業別の腎細胞がんのオッズ比

職業地位	対照 %	症例 %	オッズ比（95%信頼区間）[a,b] モデル 1	モデル 2	モデル 3
男性					
全数	111,925	2,703			
ブルーカラー産業					
ブルーカラー職	39.0	34.2	1.00	1.00	1.00
サービス職	13.5	14.2	1.26 (1.11−1.44)	1.26 (1.10−1.43)	1.26 (1.10−1.43)
専門職	4.3	5.0	1.52 (1.24−1.86)	1.53 (1.25−1.88)	1.53 (1.25−1.87)
管理職	3.2	5.8	1.62 (1.35−1.95)	1.61 (1.34−1.94)	1.61 (1.34−1.93)
サービス産業					
ブルーカラー職	4.7	4.0	1.17 (0.94−1.47)	1.18 (0.94−1.47)	1.18 (0.94−1.48)
サービス職	13.4	13.2	1.29 (1.12−1.49)	1.29 (1.12−1.49)	1.29 (1.12−1.49)
専門職	1.1	1.2	1.34 (0.94−1.92)	1.36 (0.95−1.95)	1.36 (0.95−1.95)
管理職	1.6	2.7	1.50 (1.15−1.97)	1.51 (1.15−1.97)	1.51 (1.15−1.97)
ホワイトカラー産業					
ブルーカラー職	3.6	2.0	0.78 (0.58−1.05)	0.79 (0.59−1.06)	0.79 (0.59−1.06)
サービス職	8.1	9.6	1.48 (1.25−1.75)	1.48 (1.25−1.76)	1.48 (1.25−1.76)
専門職	6.5	6.5	1.29 (1.09−1.53)	1.32 (1.11−1.56)	1.32 (1.11−1.57)
管理職	1.0	1.7	1.47 (1.07−2.03)	1.48 (1.07−2.04)	1.48 (1.07−2.04)
女性					
全数	56,493	613			
ブルーカラー産業					
ブルーカラー職	28.9	28.1	1.00	1.00	1.00
サービス職	8.8	10.0	1.48 (1.10−2.00)	1.49 (1.10−2.01)	1.49 (1.11−2.02)
専門職	0.5	0.3	0.92	0.92	0.93

			(0.23−3.75)	(0.23−3.76)	(0.23−3.79)
管理職	0.5	0.8	1.69	1.70	1.73
			(0.69−4.15)	(0.69−4.18)	(0.70−4.25)
サービス産業					
ブルーカラー職	4.5	6.4	1.50	1.52	1.52
			(1.06−2.14)	(1.07−2.16)	(1.07−2.17)
サービス職	28.2	28.1	1.18	1.20	1.21
			(0.95−1.47)	(0.97−1.50)	(0.97−1.50)
専門職	0.8	1.0	1.81	1.82	1.83
			(0.79−4.12)	(0.80−4.14)	(0.80−4.18)
管理職	0.6	1.1	1.91	1.97	1.99
			(0.89−4.11)	(0.91−4.23)	(0.92−4.27)
ホワイトカラー産業					
ブルーカラー職	0.9	1.0	1.35	1.35	1.36
			(0.59−3.07)	(0.59−3.08)	(0.60−3.09)
サービス職	12.0	12.9	1.37	1.38	1.39
			(1.04−1.81)	(1.05−1.82)	(1.05−1.84)
専門職	14.5	10.4	0.98	0.98	0.99
			(0.73−1.32)	(0.73−1.32)	(0.73−1.33)
管理職	-	-	-	-	-

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

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

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。
（方法）
関東労災病院において経尿道的膀胱腫瘍切除術の際に腫瘍を一部採取し、ゲノムを抽出、精製した。それらのゲノムを鋳型にして ZNF668 遺伝子の Exon1, 2, 3 の近傍の intron 配列より作製したプライマーを用い、PCR 法にて Exon1, 2, 3 を増幅した。更にそれらの PCR プライマーを用いてダイレクトシークエンシング法にて Exon1, 2, 3 の塩基配列を決定した。また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。
（結果）
膀胱腫瘍ゲノムにおける ZNF668 遺伝子解析：Exon1 では既知の一塩基多型（SNP）としては rs230322、rs959313015、rs192022056 において変異が見られた。既知の SNP 以外にも変異を疑うシークエンス波形が見られた。Exon2 では既知の SNP としては rs2303223 が見られた。Exon3 では既知の SNP としては rs756586541、rs763330703、rs768496978 が見られた。膀胱腫瘍組織における ZNF668 蛋白発現解析： ZNF668 蛋白は膀胱癌細胞では主に核に存在している。膀胱癌でも悪性度の低いものでは ZNF668 の染色性がよく、悪性度の高いもので染色の強さ、染色細胞の割合が低かった。
（結論）
膀胱腫瘍ゲノムには ZNF668 遺伝子変異が見られる可能性がある。また ZNF668 蛋白の細胞核における発現は悪性度の高い膀胱癌で発現が低下していた。

A.　研究目的

膀胱腫瘍の発生にはタバコ、アルコール飲酒、職業による化学薬品等の有害物質への曝露による環境因子と一塩基多型に代表される生殖細胞由来の遺伝性因子の双方が重要と考えられる。前者では有害

な環境因子によって膀胱尿路上皮に体細胞変異が生じ、それらが蓄積して driver となることにより膀胱腫瘍が生じる。従って膀胱腫瘍のゲノムにどのような体細胞変異が起こっているかを解析することは膀胱腫瘍の病因論的に重要である。

我々は環境因子による体細胞変異、および生殖細胞由来の遺伝性因子を検討するために、膀胱癌患者の血液ゲノムと膀胱腫瘍ゲノムの採取、保存を行っている。現在まで血液ゲノムは約 200 例、膀胱腫瘍ゲノムは約 100 例を保存している。

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

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 遺伝子の Exon1, 2, 3 の近傍の intron 配列より作製したプライマーを用い、PCR 法にて Exon1, 2, 3 を増幅した。更にそれらの PCR プライマーを用いてダイレクトシークエンシング法にて Exon1, 2, 3 の塩基配列を決定した。使用したプライマーは表１に示す。

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 (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。

（倫理面への配慮）

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

C.　研究結果

膀胱腫瘍ゲノムにおける ZNF668 遺伝子解析

未だ解析は進行中である。PCR 法による ZNF668 遺伝子 Exon の増幅は図１に電気泳動写真を示す。PCR 産物のダイレクトシークエンシングによって、Exon1 では既知の一塩基多型（SNP）としては rs230322、rs959313015、rs192022056 において変異が見られた（図２）。既知の SNP 以外にも変異を疑うシークエンス波形が見られた

（図３）。Exon2 では既知の SNP としては rs2303223 が見られた。Exon3 では既知の SNP としては rs756586541、rs763330703、rs768496978 が見られた。

膀胱腫瘍組織における ZNF668 蛋白発現解析

未だ解析は進行中である。Preliminary な結果としては、ZNF668 蛋白は膀胱癌細胞では主に核に存在している。膀胱癌でも悪性度の低いものでは ZNF668 の染色性がよく、悪性度の高いもので染色の強さ、染色細胞の割合が低かった（図４）。

D.　考察

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

膀胱腫瘍組織における ZNF668 蛋白発現は悪性度の高い癌で発現が低下している可能性がある。このことは ZNF668 が癌抑制遺伝子として作用しているという仮説に矛盾しない。

E.　結論

膀胱腫瘍ゲノムには ZNF668 遺伝子変異が見られる可能性がある。また ZNF668 蛋白の細胞核における発現は悪性度の高い膀胱癌で発現が低下していた。

F. 健康危険情報

（総括研究報告書に記載）

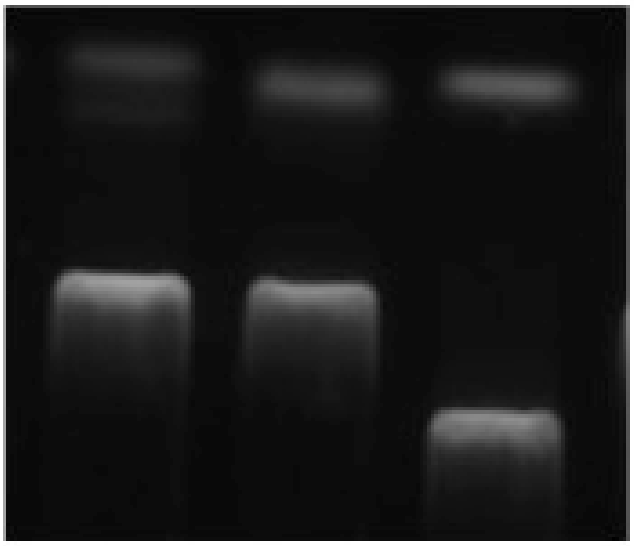
G.　研究発表

未発表

H.　知的財産権の出願・登録状況

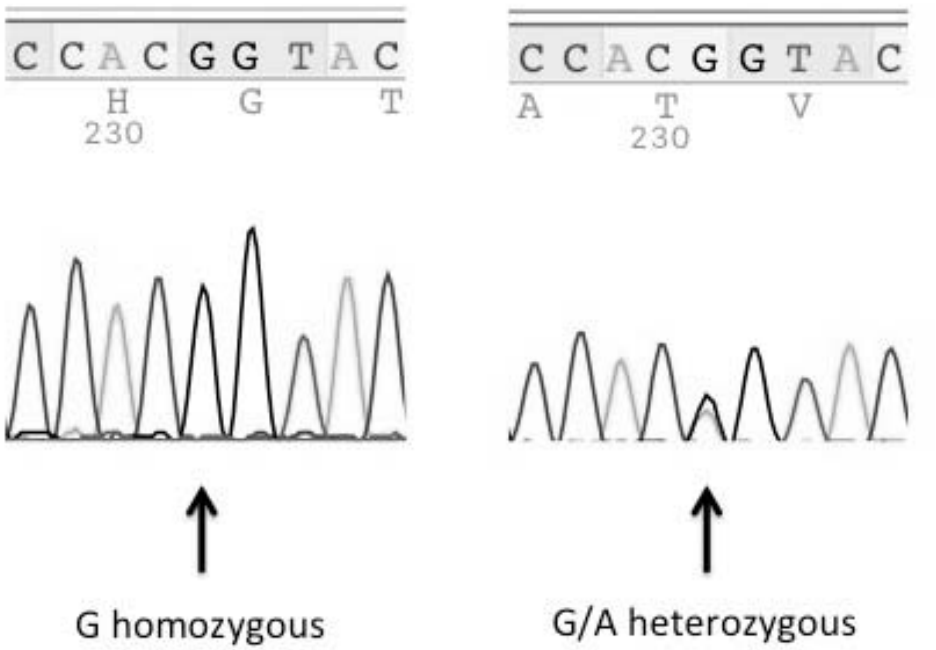
なし

図１：PCRによるZNF668遺伝子の増幅



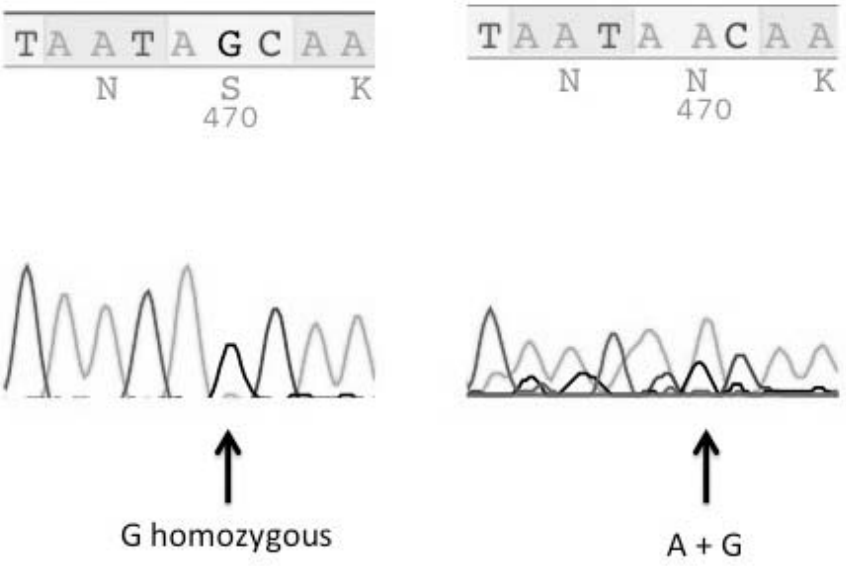
Ex1　　Ex2　　Ex3

図2



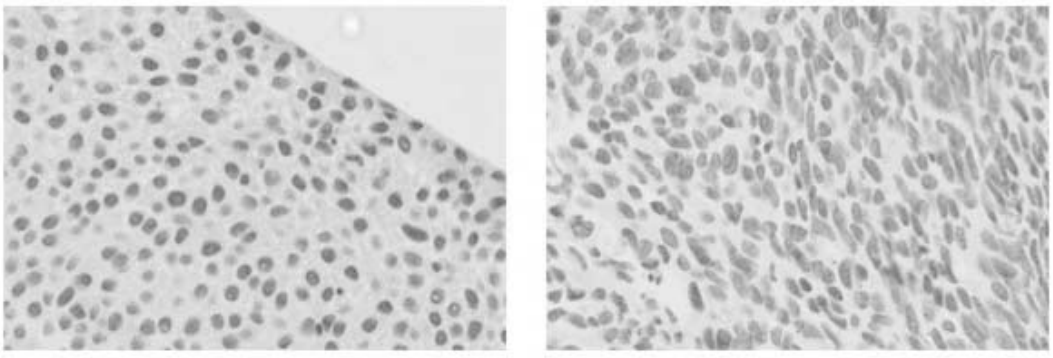
SNP Rs2303222部位のシークエンシング波形。
左膀胱腫瘍はG/G、右はG/Aのアリルを示す。

図3



シークエンシング波形。左膀胱腫瘍はG/G、右はA+Gを示し、G➡Aの体細胞変異の可能性あり。

図4



ZNF668蛋白の組織染色。左膀胱腫瘍では核に発現しているが、右膀胱腫瘍では核の発現は乏しい。

表１：ZNF668 遺伝子の増幅に用いたプライマー

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

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

近年、種々の悪性腫瘍や疾患の原因となる化学物質などの環境因子の重要性と、それらの病態について新たな視点で検討する必要性が提起されている。しかし、未だ未規制化学物質に対する健康障害予防対策は万全ではなく、安衛法第 22 条の「健康障害を防止するための必要な措置を講じる」ためのリスクアセスメントの対象特定方法についても議論は十分でない。そこで、労働環境がもたらす疾病リスクを大規模医療データから推定し、新たなリスクアセスメント対象の糸口を掴むことを目的とした。

（1）（独）労働者健康安全機構の入院患者病職歴データベースを用い、各産業の各種癌に対するオッズ比を算出した。共変量を調整した結果、第一次産業において、いくつかの種癌に対するオッズ比が 0.66-0.85（腎癌、尿管癌、膀胱癌、食道癌、肝臓癌、膵臓癌、大腸癌、肺癌、乳癌）と他産業より低く、第三次産業では 1.07–1.49（精巣癌、尿管癌、膀胱癌、肝臓癌、大腸癌）と有意に高かった。

（2）神奈川県悪性新生物登録事業より、職業癌となりうる胆管癌を用いて臨床疫学的特徴の解析を行った。2003 年には 22%であった 3 年生存率は、2009 年には 41%と年代と共に予後が改善した。また肝内胆管癌（C221）と肝外胆管癌（C240、C241）では発生年齢や予後に差があり、病理組織型によっても予後の差を認めた。予後良好な因子は、肝外胆管であること、若年であること、非腺癌であることなどであった。

（3）神奈川県悪性新生物登録事業より、肝細胞癌の予後の経年変化及び施設間格差、地域集積性について検討した。登録症例数の多い施設の 5 年生存率は、1 施設を除いて有意差は認めなかった。また初発登録時に stage4 である割合は、県内港湾部の施設で高い傾向があった。

今後、これらの情報をもとに、更に詳細な分析を行い、労働環境管理、リスクアセスメントに繋がる知見を探索する。

A. 研究目的

アスベスト取扱業と肺癌や印刷業に関する胆管癌など、近年、職業由来の発癌の報告が散見され、種々の悪性腫瘍や疾患に対する化学物質の重要性とそれらの病態について新たな視点で検討する必要性が提起されている。しかし対象物質や対象環境の特定方法についてはまだ十分な議論がされていない。職業疾病の臨床像についても、職業の関連の蓋然性が高くとも、不明な点が多く、職業疾病を浮き彫りにする糸口を見出すことは極めて困難な作業である。

今回の研究では、働く人々の労働環境と疾病の関連について、大規模医療データを用いて臨床的、疫学的に解析することで、リスクアセスメントの対象を探索することを目的とした。

使用する大規模医療データは、(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、人口 900 万を超える日本第二の都道府県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。これらを用いて、職業癌ハイリスクグループの網羅的解析と、既存の職業癌に関する臨床的疫学的検討を行うことを目的とした。

B. 研究方法

（1）(独）労働者健康安全機構に昭和 59 年より蓄積された全国労災病院の入院患者病職歴調査データベースを用いて、癌を中心とした各種疾病と産業との関連や、疫学的特徴を解析した。この研究では病職歴データベースに登録されている患者属性、入院の対象となった疾病、生活習慣病、嗜好歴、有機溶剤使用経験、特殊健診受診歴を利用し、患者群の分布、特性の解析を行なった。さらに、各種の癌をケースとし、年齢、性別、登録施設をマッチさせた四肢の骨折症例からコントロールを 1:1 で作成し、条件付きロジスティックモデルによって職業の各種癌に対するオッズ比を検討した。

（2）新たな職業癌として近年注目された胆管癌について、神奈川県地域がん登録を用い、腫瘍の臨床的特徴（腫瘍占拠部位、病理組織学型）について臨床的サブグループごとに、頻度の差やカプランマイヤー法を用いた予後の差を析した。

（3）癌の予後の登録施設間格差や地域特性を検討するため、登録症例数の多い消化器癌である肝臓癌を用いて、症例の属性や予後を比較した。

解析には STATA/MP14.0 software (Stata-Corp LP, College Station, TX)を用いた。

ベースライン特性は χ 2 乗検定を用いて解析した。生存時間の解析では、生存中のエンドポイントを 3 年生存率では 1095 日、5 年生存率では 1825 日とした（右側打ち切り)。死亡が確認されていない症例のうち、最終生存確認日の登録がある症例（生存期間がエンドポイント未満の症例）を脱落による打ち切り例とした。年齢調整 3 年生存率は、エンドポイントを 1095 日とし、解析対象全体の年齢階級別症例分布を用い、調整層化 Cox 生存

曲線を算出した。５年生存率は Kaplan–Meier 法を用い、Logrank 検定で有意差を検討した。死亡に関連する要因のハザード比は 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。

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消化器癌を対象とした疫学的研究」の承認を得て実施した。

C. 研究結果

（１）病職歴データベースの解析

（独）労働者健康安全機構に昭和 59 年より蓄積された入院患者の病職歴調査登録は 652 万件あり、同一症例による重複入院を初回入院に限ると 418 万件、そのうち職業の登録があるものは 183 万件であった。更に、病名を癌に限ると、主な癌腫は前立腺 4,622 例、腎臓 1,538 例、食道 2,461 例、胃 12,832 例、肝臓 3,360 例、膵臓 3,314 例、胆管 1,889 例、大腸 13,502 例、肺 9,182 例、乳房 5,294 例であった。

四肢の骨折患者を用いた 1:1 の症例対照研究により、各癌種の産業別のオッズ比は、農業が腎癌、大腸癌、乳癌で 0.66(95%C.I 0.46-0.95, 0.59-0.73, 0.53-0.83)から肺癌 0.85（95%C.I 0.74-0.97）、建設業が前立腺癌で 0.69(95%C.I 0.62-0.73) から大腸癌で 0.91(95%C.I 0.85-0.98)と、他の業種より低い傾向が見られた。また、農業、林業、漁業の第一次産業をまとめると、乳癌 0.60(C.I 0.49-0.75)から肺癌 0.83(95%C.I 0.74-0.95)と他の産業に比して低く、第三次産業では肝臓癌 1.12(95%C.I 1.01-1.24) 、 大腸癌 1.13(95%C.I 1.07-1.19)等、高い傾向にあった。肉体労働の多い農業、漁業、鉱業、建設業をまとめると、各癌種のオッズ比は、精巣、腎、尿管、膀胱、胃、肝臓、膵臓、胆管、大腸、肺、乳のいずれに於いても有意に低かった（表１）。

特殊検診を受けたものは 19,377 例あり、そのうち建設業者が 2,928（15.1%）、製造業が 10,136 例（52.3%）を占めた。Blue collar ではない公務も 1,237 例（6.38%）と他の職種よりも登録数が多かった。各種癌症例で、特殊健診の受診率の割合を検討すると、特殊検診を受けている者の割合は、癌患者群が、骨折に比して少ない傾向を認めた。

（２）地域がん登録を用いた胆管癌の解析

1976 年から 2013 年に登録された胆管癌は 14,287 件であった。内訳は肝内胆管癌(C221)、肝外胆管癌（C240)、ファーター乳頭癌(C241)がそれぞれ 3,369(23.6%)例、 9,285（65.0%)例、1,633 (11.4%)例であった。

全体の平均診断時年齢は 71.4 歳（SD 11.5)、平均死亡時年齢は 72.8 歳(SD 11.4)であった（表 2)。

＜生存率の変遷＞

２年ごとの年齢調整３年生存率は、2003 年

から 2004 年では 22.0%であったが、2007 年から 2008 年では 28.4%、2009 年から 2010 年では 41.0%へ上昇した（図 1)。

胆管癌の腫瘍占拠部位ごとの５年生存率は、肝内胆管癌では 5.5%(2005 以前)から 20.3%（2006-2013）へ改善し、肝外胆管癌も 8.7%から 29.4%へ改善を認めた。

＜病理組織型＞

病理組織型が特定可能であった症例は 5,481 例であった。肝内胆管癌は肝外胆管癌に比べ、若年性の頻度が高く（$p < 0.01$)、 手術を受ける頻度が少なかった($p < 0.01$)。病理組織学的結果では, 肝内胆管癌では肝外胆管癌に比して非腺癌症例の割合が多かった($p < 0.05$)。

全死亡について診断時期、診断時年齢、性別、腫瘍占拠部位、病理組織型、手術の有無で調整した各要因のハザード比を算出した。肝外胆管癌に対する肝内胆管癌のハザード比は有意に高かった (HR 1.38, 95% CI 1.31–1.53)。 腺癌に対する非腺癌のハザード比は有意に低かった(HR 0.71, 95% CI 0.54–0.96)。非手術症例に対する手術症例のハザード比は有意に低かった(HR 0.52, 95% CI 0.51–0.58)（表 3)。

TNM 分類による病期が得られた 1,897 例で、病期を含めた全死亡のハザード比について追加解析を行った。有意差が認められたのは診断時期 0.70 (95% CI 0.53–0.94)、80 歳以上 1.98 (95% CI 1.38–2.84)、腫瘍占拠部位 1.46 (95% CI 1.28–1.67)、病理組織型 0.39 (95% CI 0.19–0.78)、手術の有無 0.69 (95% CI 0.61–0.78)、TNM 分類による病期 3.18 (95% CI 2.78–3.65)であり、TNM 病期分類を含めても、主要な結果は変わらなかった。

（３）地域がん登録を用いた肝細胞癌の解析

2013 年末までに神奈川県地域がん登録に登録された初発肝細胞癌で生存期間が解析可能な症例は 40,276 例であった。これらのうち、登録症例数が上位 15 位に入る症例につき、5 年生存率を施設ごとに算出したものが図 2 である。該当施設間の予後の差が、lead time bias に影響されている可能性を考慮し、病期分類のある症例に限って頻度を検討すると、stage4 の占める割合の高い施設は、県内の港湾部に位置していた（表 4)。

D. 考察

（１）労災病院病職歴データベースを用いた研究

本研究では、日本産業分類コードを用いて、20 の分類に従って産業と疾病のリスクを検討した。現段階で、産業ごとの癌のリスクは、肉体作業の労働量と関連していることが推定される。言い換えると blue collar と white collar の特徴と置き換えられるかもしれない。本研究の最終目標は、職業癌をもたらす有害な暴露物質を探求することであるが、有害物質のみならず、業務に伴う肉体作業等の作業態様が癌のリスクとなりうる可能性も検討すべきと考えられる。第３次産業の割合が増加する現代社会の業務体系が、労働者の癌のリスクを全般に高めている可能性も否定できない。

今回の研究では、病職歴のうち、就労期間が最長のものを用いて解析を行った。しかし、

職業癌は、最長就労職業ではなく、また現職ではない職業が原因となっていることも多い。更に、大気中の有害化学物質の 9 割は製造業から排出されており、今後製造業を中心とした、更に細かい業種での分析を行う。

（2）地域がん登録を用いた胆管癌の解析

胆管癌の予後は、腫瘍占拠部位と病理組織型によって統計学的有意差を持って異なっており、時代とともに予後の顕著な改善が見られた。職業癌としての胆管癌は、通常の胆管癌と発症年齢や、腫瘍形態、病理組織型など多くの点に於いて異なることが報告されている。

＜腫瘍占拠部位と予後＞

本研究では神奈川県がん登録という大規模データベースをもとに、肝内胆管癌の予後は肝外胆管癌よりも短いことを示した。肝内胆管癌が肝外胆管癌よりも若年で発症するにも関わらずこの結果が得られたということは、発見時の病期と加療方法の差の影響が強いと予測される。肝外胆管癌では閉塞性黄疸が診断契機になることが多い一方、肝内胆管癌は症状も兆候も無く病期が進展し、発見が遅れるという傾向が強い。手術の根治成績が、わずかに肝外胆管癌で高いことも、肝外胆管癌の予後が良いことの一因と予測される。

職業性胆管癌は若年発症であり、第２次分枝より末梢の肝内胆管に集積している特徴があった。職業性胆管癌の予後が不良であることは、本研究で得られた様な、非職業性であっても存在する腫瘍占拠部位による予後の差も反映されている可能性がある。

＜病理組織型と予後＞

胆管癌は、殆どを占める腺癌と少数の稀な組織型から成るが、組織型が特定できない症例も多く、組織型に基づいた予後の報告は稀である。本研究で、病理組織型は肝内胆管癌と肝外胆管癌で明確な違いが認められた。胆管癌は、手術不可能である場合に病理組織型を特定する事が難しい。本研究では、非腺癌であること、手術施行例であることが、他のリスク要因と独立して予後良好の因子であった。職業性胆管癌では、その非腫瘍部位に BilIN や IPNB が見られること、その中にはγH2AX のような DNA 損傷を示唆する免疫組織学的反応が高頻度に発現すること、また PD-L1 抗体の発現亢進などが報告されている。本研究でも、組織学的特徴が予後の差に関連している可能性があり、職業癌は、組織の点からも通常の癌と異なる予後を辿る可能性を示唆するものと考える。

（3）地域がん登録を用いた肝臓癌の解析

神奈川県の肝細胞癌の予後は、全体として経年とともに改善していたが、施設間格差を認めた。予後が良い施設は、新たな診断治療デバイスを着実に使いこなすことでより効果的に生存期間を延ばしている可能性があり、積極的な新技術の導入と応用が良好な結果につながることが考えられる。一方で、肝細胞癌は、慢性肝炎に対する丹念なフォローの上で微小な初発肝癌が見つかることが多く、施設間格差が lead time bias によって生じている可能性を考えた。そこで、登録症例の病期別分布を調べた結果、港湾部で初発登録時に進行病期である症例が多いことが判明した。

この点は､神奈川県内のsocioeconomic statusの影響を考慮する必要があるだろう。

癌に限らず、職業疾病は、労働環境と直接関連するリスク因子の他、その産業に従事する者の置かれるsocioeconomic statusが強く影響する。今後は産業によるlead time biasの調査も検討したい。

（4）研究の限界

本研究の限界としては、労災病院病職歴データベース、地域がん登録ともに選択バイアスの存在が挙げられる。病職歴データベースは、全国労災病院に入院した患者に限られている。施設が全国に分布しているため、施設間の調整が可能であり、地域のバイアスは除くことができた。一方で、入院症例に限られているため、近年、健診や産業医の普及などで早期発見、外来加療可能であった癌については含まれていない。また、病院ごとの該当医療圏で担う役割によって、各施設の患者の特性が偏っている可能性もある。さらに、癌種によっては症例数がきわめて少なく、細分化した解析は適切でない可能性がある。

地域がん登録は、全数調査を前提としているが、登録漏れは必ず存在する。しかし、本研究で用いた神奈川県地域がん登録全体のDCOは18.2%であり、がん登録の信頼性の基準である20%を下回っているため、大きな選択バイアスが存在するとは言えない。また、登録施設ごとに得意とする治療法の偏り、施設ごとに集まる病期の偏り、施設内での登録症例の偏りが予後に影響している可能性がある。治療方法についての情報が、簡易な登録に留まり、欠損値も多いため、予後に直接何が具体的に影響したか、また因果の強さを検討することができない点も限界として挙げられる。

E. 結論

本研究で、各種癌のリスクが、従事する産業によって異なる可能性が示唆された。また、職業癌の特殊な病態が、一般の癌の特性と異なる可能性も示唆された。

職業疾病に関する疫学研究は、疾病の発症が集積し、その原因となる要因を明らかにすることで積み重ねられる。これまで集積されてきた大規模医療データを用いることで、職業疾病とそのリスク要因の手がかりを得ることは有用な試みと考えられる。引き続き、新たなリスクアセスメント対象となる化学物質の特定まで、詳細な検討を加えて行く。

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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H. 知的財産権の出願・登録状況

なし

表1：癌腫ごとの各産業のOdds比

産業分類	農業	漁業	鉱業	建設業	製造業	電気ガス
癌腫						
症例数						
陰茎	3.09(0.43-21.8)	-	-	1.41(0.47-4.23)	0.69(0.25-1.91)	-
59	3	0	0	12	13	0
前立腺	0.94(0.77-1.12)	0.86(0.63-1.18)	1.31(0.80-2.12)	0.69(0.62-0.78)	1.00(0.92-1.10)	1.13(0.78-1.67)
4,622	246	81	41	575	1377	60
精巣	0.13(0.15-1.13)	2.92(0.23-28.5)	1.08(0.64-18.4)	0.55(0.35-0.93)	0.95(0.64-1.42)	0.73(0.16-3.33)
291	2	3	1	32	69	3
腎	0.66(0.46-0.96)	0.92(0.55-1.54)	1.48(0.51-4.36)	0.84(0.70-1.07)	1.05(0.89-1.24)	0.84(0.39-1.88)
1,538	57	30	8	185	418	14
尿管	0.65(0.43-0.93)	0.42(0.20-0.85)	1.79(0.32-10.1)	0.72(0.55-0.93)	1.01(0.86-1.30)	0.44(0.15-1.25)
1,033	59	13	5	133	273	6
膀胱	0.82(0.69-0.96)	0.77(0.57-1.03)	1.35(0.82-2.24)	0.82(0.74-0.91)	1.08(1.00-1.18)	0.69(0.48-0.99)
6,245	321	87	39	798	1797	51
副腎	1.24(0.13-11.9)	-	-	1.88(0.34-10.3)	3.04(0.85-10.9)	-
50	2	0	0	8	18	0
食道	0.73(0.55-0.97)	0.85'0.55-1.31)	1.46(0.73-2.94)	0.94(0.79-1.12)	1.11(0.96-1.27)	0.64(0.35-1.20)
2,461	104	51	22	374	723	22
胃	0.95(0.86-1.06)	0.67(0.56-0.80)	0.93(0.69-1.26)	0.85(0.78-0.91)	1.09(1.03-1.16)	1.21(0.94-1.56)
12,832	846	185	89	1628	3420	134
肝臓	0.75(0.59-0.94)	0.70(0.48-1.06)	0.90(0.51-1.61)	0.87(0.75-1.01)	1.00(0.89-1.12)	(1.21(0.74-1.98)
3,360	169	47	25	472	845	40
膵臓	0.78(0.64-0.99)	0.85(0.57-1.26)	0.75(0.36-1.53)	0.82(0.70-0.97)	1.10(0.98-1.25)	0.93(0.52-1.66)
3,114	198	56	15	350	808	24
胆管	0.97(0.75-1.22)	0.54(0.32-0.92)	1.18(0.59-2.35)	0.77(0.63-0.94)	1.10(0.94-1.29)	1.01(0.49-2.07)
1,889	172	24	18	219	479	15
大腸	0.66(0.59-0.73)	0.85(0.69-1.04)	1.33(0.99-1.78)	0.91(0.85-0.98)	0.99(0.93-1.05)	0.88(0.69-1.13)
13,502	717	199	111	1642	3400	125
肺	0.85(0.74-0.97)	0.83(0.64-1.07)	1.43(1.01-2.05)	0.89(0.81-0.98)	1.22(1.14-1.32)	0.96(0.70-1.31)
9,182	520	149	101	1311	2560	86
乳	0.66(0.53-0.83)	0.27(0.13-0.56)	-	1.04(0.85-1.27)	1.13(1.02-1.25)	1.43(0.75-2.71)
5,494	164	10	2	207	1028	24
子宮頸	0.97(0.49-1.91)	-	-	1.19(0.69-2.05)	0.94(0.74-1.18)	0.19(0.02-1.73)
962	21	1	0	30	154	1
子宮体	0.79(0.46-1.38)	-	-	1.04(0.65-1.67)	0.96(0.76-1.19)	0.74(0.16-3.32)
1,055	28	0	0	36	186	3
白血病	1.15(0.60-2.23)	1.07(0.45-2.53)	0.62(1.44-2.67)	0.63(0.42-0.93)	1.12(0.83-1.49)	1.06(0.23-4.88)
529	26	13	3	55	151	4

骨折症例43,338例に対し、性別、5歳ごとの年齢区分、登録施設を調整した1:1のケースとコントロールを用い、喫煙、飲酒、生活習慣病、職業で条件付きロジスティック検定を施行した。

表1:癌腫ごとの各産業のOdds比　続

産業分類	情報通信	運輸	卸　小売	金融保険	不動産	学術サービス
癌腫						
症例数						
陰茎	–	1.11(0.22–5.57)	2.95(0.54–16.3)	0.34(0.44–2.58)	2.94(0.10–85.2)	2.92(1.06–8.08)
59	1	5	9	2	1	3
前立腺	1.50(1.03–2.20)	0.93(0.82–1.07)	1.17(1.02–1.34)	1.45(1.09–2.03)	0.61(0.39–0.94)	1.05(0.79–1.40)
4,622	69	478	503	106	36	108
精巣	1.3(0.56–3.04)	0.98(0.56–1.71)	1.31(0.81–2.14)	0.47(0.16–1.41)	1.38(0.30–6.29)	2.31(0.81–6.63)
291	14	28	40	5	5	12
腎	2.62(1.38–5.00)	0.79(0.61–1.05)	1.15(0.93–1.42)	1.25(0.82–1.92)	0.79(0.42–1.45)	1.42(1.12–2.93)
1,538	35	114	201	50	18	50
尿管	1.14(0.42–3.13)	0.99(0.72–1.37)	1.19(0.89–1.60)	1.28(0.75–2.18)	0.64(0.33–1.24)	1.78(0.89–3.59)
1,033	9	84	114	36	17	23
膀胱	1.16(0.80–1.69)	1.01(0.89–1.12)	1.16(1.03–1.29)	1.04(0.82–1.35)	0.57(0.40–1.82)	1.07(0.83–1.39)
6,245	62	687	783	137	51	127
副腎	–	2.56(0.37–17.6)	0.24(0.5–1.12)	38.5(0.87–1694)	–	–
50	0	6	5	1	0	0
食道	0.96(0.49–1.89)	0.94(0.77–1.15)	1.12(0.92–1.36)	0.83(0.54–1.25)	1.27(0.81–2.27)	0.63(0.38–1.02)
2,461	20	251	278	48	31	30
胃	1.13(1.89–1.44)	1.08(0.99–1.18)	1.11(1.03–1.20)	0.9(0.76–1.04)	0.77(0.61–0.97)	1.07(0.89–1.23)
12,832	147	1212	1639	263	136	249
肝臓	1.02(0.64–1.75)	1.19(1.01–1.42)	1.01(0.93–1.27)	0.94(0.67–1.33)	0.76(0.50–1.15)	0.95(0.66–1.36)
3,360	29	341	401	68	43	63
膵臓	1.68(1.06–2.66)	0.97(0.81–1.16)	1.17(1.00–1.36)	0.88(0.60–1.27)	0.94(0.58–1.50)	1.41(0.56–2.08)
3,114	50	270	418	57	35	62
胆管	1.13(0.73–2.47)	1.01(0.80–1.28)	1.16(0.94–1.41)	0.94(0.61–1.44)	0.89(0.41–1.53)	0.81(0.51–1.29)
1,889	26	162	228	41	16	33
大腸	1.14(0.9–1.46)	1.20(1.10–1.32)	1.17(1.09–1.26)	0.99(0.84–1.16)	0.98(0.79–1.21)	1.41(1.18–1.69)
13,502	142	1231	1887	291	172	293
肺	0.69(0.49–0.96)	1.04(0.94–1.17)	0.90(0.82–1.00)	0.92(0.74–1.16)	0.78(0.57–1.05)	1.07(0.83–1.37)
9,182	68	889	1062	180	95	148
乳	0.93(0.68–1.28)	1.21(0.95–1.56)	1.15(1.04–1.27)	0.99(0.81–1.19)	1.23(0.88–1.72)	1.09(0.78–1.33)
5,494	78	140	1095	218	78	110
子宮頸	0.86(0.38–1.96)	0.99(0.59–1.67)	1.15(0.92–1.45)	1.10(0.71–1.73)	0.49(0.21–1.15)	0.62(0.33–1.19)
962	11	30	204	45	8	15
子宮体	0.73(0.31–1.73)	1.75(0.90–3.41)	1.22(0.99–1.50)	1.01(0.67–1.52)	0.76(0.40–1.42)	0.79(0.44–1.41)
1,055	9	25	244	52	18	21
白血病	2.07(0.77–5.59)	1.34(0.8602.11)	0.91(0.63–1.31)	0.61(0.27–1.36)	1.03(0.31–3.48)	1.52(0.58–4.02)
529	12	48	61	10	5	11

表1:癌腫ごとの各産業のOdds比　続

産業分類	宿泊飲食	生活娯楽	教育学習	医療福祉	複合サービス	サービス業	公務
癌腫							
症例数							
陰茎	−	−	0.22(0.2−2.48)	1.54(0.80−29.9)	4.17(0.25−68.3)	−	1.66(0.32−8.49)
59	0	1	1	1	2	0	5
前立腺	0.67(0.44−0.85)	0.83(0.59−1.18)	1.69(1.34−2.11)	1.31(0.95−1.79)	0.96(0.68−1.34)	0.86(0.67−1.09)	1.51(1.25−1.82)
4,622	57	60	218	94	72	132	309
精巣	1,72(0.55−5.32)	0.70(0.19−2.53)	1.25(0.46−3.36)	1.34(0.63−2.85)	2.45(0.63−9.56)	1.24(0.59−2.59)	0.80(0.39−1.62)
291	8	4	10	16	7	18	14
腎	0.97(0.68−1.39)	0.79(0.47−1.31)	0.84(0.55−1.28)	0.83(0.58−1.19)	1.05(0.47−2.35)	0.95(0.66−1.35)	1.38(0.96−1.98)
1,538	64	29	42	61	12	64	77
尿管	2.24(1.33−3.75)	0.88(0.52−1.48)	1.19(0.69−2.07)	1.08(0.65−1.79)	0.99(0.40−2.47)	1.29(0.82−2.05)	1.19(0.80−1.76)
1,033	56	30	28	31	9	1.29	62
膀胱	0.91(0.73−1.14)	1.07(0.83−1.37)	1.09(0.89−1.35)	1.20(0.98−1.48)	1.33(0.95−1.84)	0.92(0.75−1.12)	0.99(0.84−1.18)
6,245	169	143	199	219	88	196	300
副腎	1.04(0.06−17.4)	1.47(0.20−10.7)	−	−	1.67(0.11−24.3)	7.07(0.32−154.3)	−
50	1	4	0	1	1	3	0
食道	1.66(1.20−2.31)	0.67(0.46−0.99)	1.22(0.86−1.81)	0.84(0.53−1.30)	1.59(0.81−3.08)	0.81(0.58−1.13)	1.08(0.80−1.45)
2,461	127	53	73	41	24	73	116
胃	1.09(0.95−1.25)	0.95(0.81−1.12)	0.96(0.84−1.09)	0.84(0.74−0.96)	0.83(0.66−1.04)	0.83(0.73−0.96)	1.19(1.05−1.35)
12,832	463	315	448	491	141	428	598
肝臓	1.13(0.89−1.45)	0.81(0.60−1.08)	1.31(1.01−1.71)	1.07(0.80−1.43)	1.26(0.78−2.06)	0.86(0.67−1.11)	1.22(0.95−1.58)
3,360	166	94	130	108	37	135	147
膵臓	0.71(0.55−0.93)	0.93(0.70−1.23)	1.38(1.05−1.81)	1.40(0.93−1.54)	0.65(0.39−1.01)	0.83(0.64−1.07)	1.04(0.81−1.35)
3,114	109	109	138	144	29	114	128
胆管	0.79(0.59−1.09)	1.14(0.77−1.68)	1.14(0.82−1.59)	0.74(0.53−1.04)	1.54(0.92−2.58)	1.17(0.81−1.67)	1.34(0.95−1.88)
1,889	69	54	78	71	38	68	78
大腸	1.04(0.93−1.18)	0.92(0.79−1.06)	0.89(0.80−1.02)	1.03(0.91−1.13)	0.79(0.63−1.00)	0.90(0.79−1.02)	1.14(1.00−1.29)
13,502	580	388	505	677	133	467	542
肺	1.08(0.91−1.28)	0.93(0.77−1.12)	0.86(0.72−1.03)	1.09(0.92−1.28)	1.01(−.75−1.35)	0.93(0.78−1.10)	0.97(0.82−1.14)
9,182	388	246	234	355	103	344	343
乳	0.90(0.79−1.04)	1.04(0.89−1.23)	1.00(0.86−1.17)	0.86(0.77−0.95)	1.31(0.91−1.90)	0.82(0.67−0.99)	0.91(0.70−1.16)
5,494	410	308	374	860	67	202	119
子宮頸	1.89(1.31−2.75)	1.61(1.06−2.43)	0.57(0.39−0.85)	0.84(0.66−1.06)	0.97(0.31−2.94)	1.09(0.65−1.85)	0.53(0.24−1.19)
962	103	66	47	177	6	34	9
子宮体	1.02(0.71−1.48)	0.81(0.54−1.22)	0.79(0.54−1.12)	1.06(0.85−1.33)	1.15(0.48−2.71)	0.75(0.48−1.16)	1.27(0.66−2.44)
1,055	67	43	58	193	11	40	21
白血病	0.98(0.54−1.80)	1.21(0.61−2.41)	1.57(0.83−2.95)	0.78(0.41−1.48)	0.82(0.25−2.72)	0.59(0.32−1.08)	1.47(0.74−2.94)
529	24	19	26	18	5	17	21

表1:癌腫ごとの各産業のOdds比　続

産業分類	第一次産業	第二次産業	第三次産業	重労働作業	座位作業
癌腫					
症例数					
陰茎	1.57(0.28-8.82)	0.95(0.41-2.19)	0.84(0.38-1.86)	1.50(0.57-3.97)	1.01(0.33-3.16)
59	3	25	26	15	11
前立腺	0.92(0.77-1.08)	0.84(0.77-0.92)	1.11(1.02-1.21)	0.75(0.67-0.83)	1.02(0.91-1.13)
4,622	327	1993	1993	943	880
精巣	0.50(0.14-1.75)	0.73(0.51-1.03)	1.49(1.06-2.09)	0.54(0.33-0.88)	1.01(0.66-1.56)
291	5	102	170	38	55
腎	0.73(0.53-0.99)	0.98(0.84-1.14)	1.04(0.90-1.21)	0.82(0.68-0.98)	0.95(0.69-1.15)
1,538	87	611	763	280	273
尿管	0.55(0.39-0.78)	0.88(0.73-1.06)	1.29(1.07-1.57)	0.62(0.51-0.78)	1.18(0.95-1.48)
1,033	72	411	488	210	219
膀胱	0.79(0.68-0.92)	0.98(0.91-1.05)	1.07(1.00-1.16)	0.80(0.73-0.88)	0.95(0.87-1.04)
6,245	408	2634	2912	1245	1207
副腎	1.24(0.13-11.9)	4.12(1.05-16.2)	0.24(0.06-0.96)	1.71(0.41-7.15)	1.44(0.32-6.57)
50	2	26	22	10	7
食道	0.76(0.59-0.97)	1.06(0.94-1.20)	0.99(0.88-1.12)	0.88(0.76-1.02)	1.12(0.96-1.31)
2,461	155	1119	1071	551	525
胃	0.988(0.94-1.04	0.98(0.94-1.04)	1.01(0.96-1.06)	0.85(0.79-0.90)	1.09(1.02-1.17)
12,832	5137	5137	6066	2748	2409
肝臓	0.73(0.59-0.89)	0.93(0.84-1.03)	1.12(1.01-1.24)	0.81(0.71-0.91)	1.16(1.03-1.32)
3,360	216	1342	1655	713	697
膵臓	0.81(0.67-0.98)	0.98(0.88-1.10)	1.06(0.96-1.19)	0.79(0.70-0.90)	0.91(0.79-1.03)
3,114	254	1173	1559	619	524
胆管	0.86(0.69-1.07)	0.96(0.84-1.10)	1.05(0.92-1.19)	0.79(0.68-0.93)	0.99(0.84-1.18)
1,889	196	716	899	433	325
大腸	0.68(0.63-0.76)	0.95(0.91-1.00)	1.13(1.07-1.19)	0.82(0.76-0.87)	1.14(1.08-1.22)
13,502	916	5153	6891	2669	2525
肺	0.83(0.74-0.95)	1.14(1.06-1.22)	0.93(0.87-0.99)	0.88(0.81-0.95)	1.01(0.94-1.10)
9,182	669	3972	4198	2081	1715
乳	0.60(0.49-0.75)	1.12(1.02-1.24)	0.99(0.91-1.08)	0.79(0.69-0.92)	0.98(0.88-1.09)
5,494	174	1237	3964	383	5494
子宮頸	1.02(0.53-1.98)	0.97(0.78-1.21)	1.07(0.87-1.33)	1.13(0.74-1.74)	1.24(0.94-1.62)
962	22	184	747	52	150
子宮体	0.76(0.44-1.31)	0.97(0.79-1.20)	1.04(0.85-1.27)	0.91(0.63-1.31)	1.11(0.85-1.44)
1,055	28	222	784	64	131
白血病	1.12(0.67-1.89)	0.87(0.67-1.14)	1.04(0.80-1.34)	0.75(0.54-1.04)	1.27(0.93-1.81)
529	39	209	260	97	98

表2. 全胆管癌患者の属性

	全体[†]	ICD10			腫瘍占拠部位	
		C221	C240	C241	肝内	肝外
N(%)	14287(100)	3369(23.6)	9285(65.0)	1633(11.4)	3369(23.6)	10918(76.4)
診断時年齢						
(Mean±SD)	71.4±11.5	69.6±11.4	72.4±11.4	69.0±11.2	69.6±11.4	71.9±11.4
死亡時年齢						
(Mean±SD)	72.8±11.4	70.6±11.4	73.8±11.3	72.0±11.7	70.6±11.4	73.5±11.3
性別						
男性	8345(58.4)	2028(60.2)	5344(57.6)	973(59.6)	2028(60.2)	6317(57.9)
女性	5942(41.6)	1341(39.8)	3941(42.4)	660(40.4)	1341(39.8)	4601(42.1)
診断時期[§]						
Period 1	10041(70.3)	2355(69.9)	6621(71.3)	1065(65.2)	2355(69.9)	7686(70.4)
Period 2	4246(29.7)	1014(30.1)	2664(28.7)	568(34.8)	1014(30.1)	3232(29.6)
手術の有無						
有	5911(41.4)	964(28.6)	3852(41.5)	1095(67.1)	964(28.6)	4947(45.3)
無	8376(58.6)	2405(71.4)	5433(58.5)	538(33.0)	2405(71.4)	5971(54.7)

[†]性別、年齢、腫瘍占拠部位、診断時期の全情報が取得できた14,287例のデータ

[§]診断時期: Period 1: 1976–2005, Period 2: 2006–2013.

表 3. 胆管癌症例における全死亡に関する各因子の調整済ハザード比

属性	ハザード比 (95% CI)[†] 全死亡	*P* 値[§]
診断時期[‡]		
Period 1	1.00(ref)	
Period 2	0.49(0.46–0.52)	<0.01**
診断時年齢		
老年性	1.00(ref)	
若年性	0.87(0.81–0.93)	<0.01**
性別		
男性	1.00(ref)	
女性	1.02(0.96–1.09)	0.43
腫瘍占拠部位		
肝外	1.00(ref)	
肝内	1.38(1.29–1.48)	<0.01**
病理組織型		
腺癌	1.00(ref)	
非腺癌	0.71(0.54–0.95)	<0.02*
手術の有無		
無	1.00(ref)	
有	0.52(0.49–0.55)	<0.01**

[†]診断時期、年齢、性別、腫瘍占拠部位、病理組織型、手術の有無の情報が得られた5481例についてCox比例ハザードモデルを用いて解析した。

[‡]診断時期: Period 1: 1976–2005, Period 2: 2006–2013.

[§] *P* 値 <0.05* あるいは <0.01** を統計学的有意とした。

表4. 登録症例数上位15位の病期分布

Rank	Hospital	N(%)		TMN stage at initial daignosis			
		Overall	Stage available	Ⅰ	Ⅱ	Ⅲ	Ⅳ
1	A	615	235	55(25.4)	107(45.5)	46(19.6)	27(11.5)
2	B	1624	100	22(22.0)	49(49.0)	20(20)	9(9)
3	C	890	6	2(33.3)	2(33.3)	1(16.7)	1(16.7)
4	D	1467	338	160(47)	107(31.7)	55(16.3)	16(4.7)
5	E	639	154	58(37.7)	36(23.4)	20(13.0)	40(26.0)
6	F	1132	185	47(25.4)	64(34.6)	48(26.0)	26(14.1)
7	G	566	9	2(22.2)	2(22.2)	4(44.4)	1(11.1)
8	H	707	215	97(45.1)	61(28.4)	46(21.4)	11(5.1)
9	I	1074	460	189(41.1)	127(27.6)	121(26.3)	23(5)
10	J	616	78	37(47.4)	23(29.5)	11(14.1)	7(9.0)
11	K	1033	312	116(37.2)	116(37.2)	57(18.3)	23(7.4)
12	L	676	128	45(35.2)	43(33.6)	31(24.2)	9(7.0)
13	M	509	25	4(16.0)	9(36.0)	8(32.0)	4(16.0)
14	N	400	95	25(26.3)	20(21.1)	29(30.5)	21(22.1)
15	O	489	57	12(21.1)	23(40.4)	19(33.3)	3(5.3)

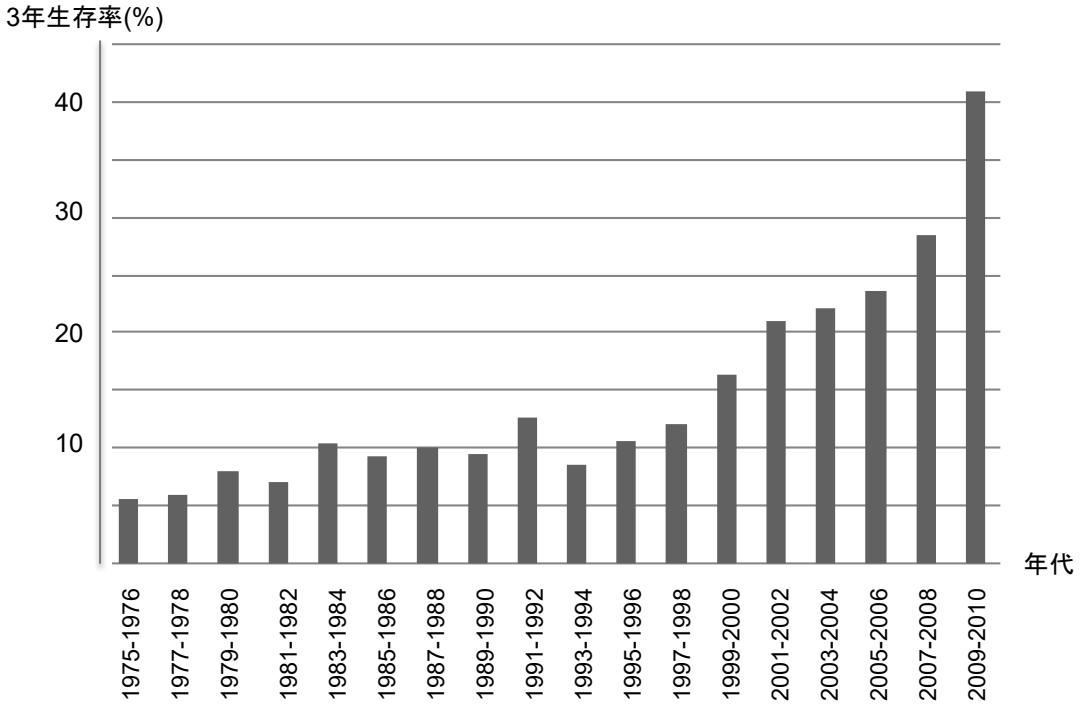

図1　2年ごとの胆管癌3年生存率の推移

対象期間中に3年経過時の生死が判明している症例について、2年ごとに区切り Kaplan-Meier法を用いた3年生存率の推移。

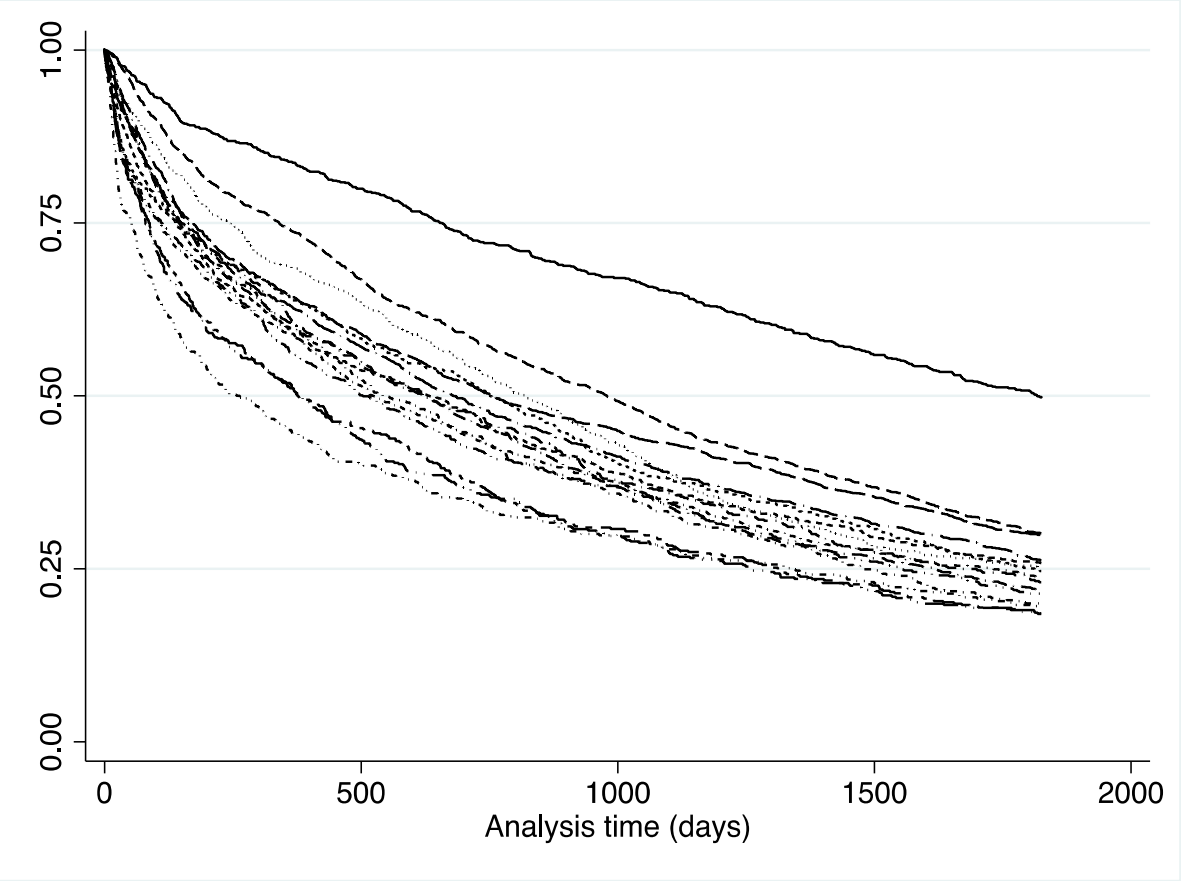

図 2 登録症例数上位 15 位の施設ごと肝細胞癌 5 年生存率

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	ページ	出版年
Zaitsu1 M, Cuevas AG, Trudel‐Fitzgerald C, Takeuchi T, Kobayashi Y, Kawachi I	Occupational class and risk of renal cell cancer	Health Science Reports	e49	doi: org/10.1002/ hsr2.49	2018
Kaneko R, Sato Y, Kobayashi Y	Cholangiocarcinoma prognosis varies over time depending on tumor site and pathology	Journal of Gastrointestinal and Liver Diseases	27 (1)	59-66	2018
Kaneko R, Nakazaki N, Omori R, Yano Y, Ogawa M, Sato Y	The effect of new therapeutic and diagnostic agents on the prognosis of hepatocellular carcinoma in Japan- an analysis of data from the Kanagawa cancer registry	Asian Pacific Journal of Cancer Prevention	18 (9)	2471-2476	2017
金子麗奈	診断治療技術の進歩が肝臓癌の予後に与えた影響をがん登録から捉える	神奈川県のがん（神奈川県立がんセンター）		24-25	2018

IV. 研究成果の刊行物・別刷

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RESEARCH ARTICLE

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Occupational class and risk of renal cell cancer

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Abstract

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

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

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

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

KEYWORDS

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

1 | INTRODUCTION

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

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

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

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

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

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

2 | MATERIALS AND METHODS

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

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

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

FIGURE 1 Occupational class cross-classified with industrial cluster

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

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

2.1 | Cases and controls

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

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

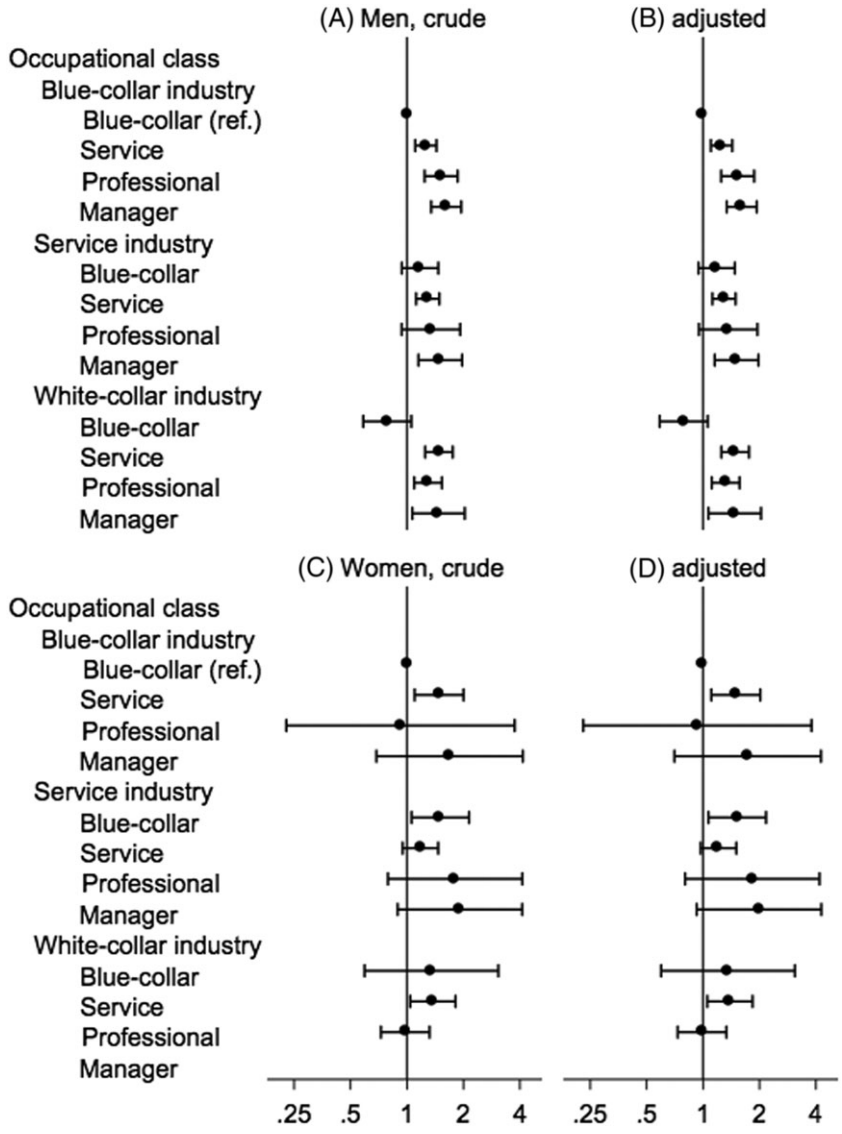

FIGURE 2 Odds ratios for renal cell cancer across different occupational classes stratified by sex. The odds ratio (dot) and 95% confidence interval (bar) were estimated by unconditional logistic regression with 5 imputed data. Male and female odds ratios were (A, C) adjusted for age and year of admission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

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

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

(Continues)

TABLE 1 (Continued)

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

Abbreviation: NA, not available.

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

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

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

2.2 | Occupational class defined by occupational and industrial category

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

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

2.3 | Covariates

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

2.4 | Statistical analysis

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

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

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

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

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

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

3 | RESULTS

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

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

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

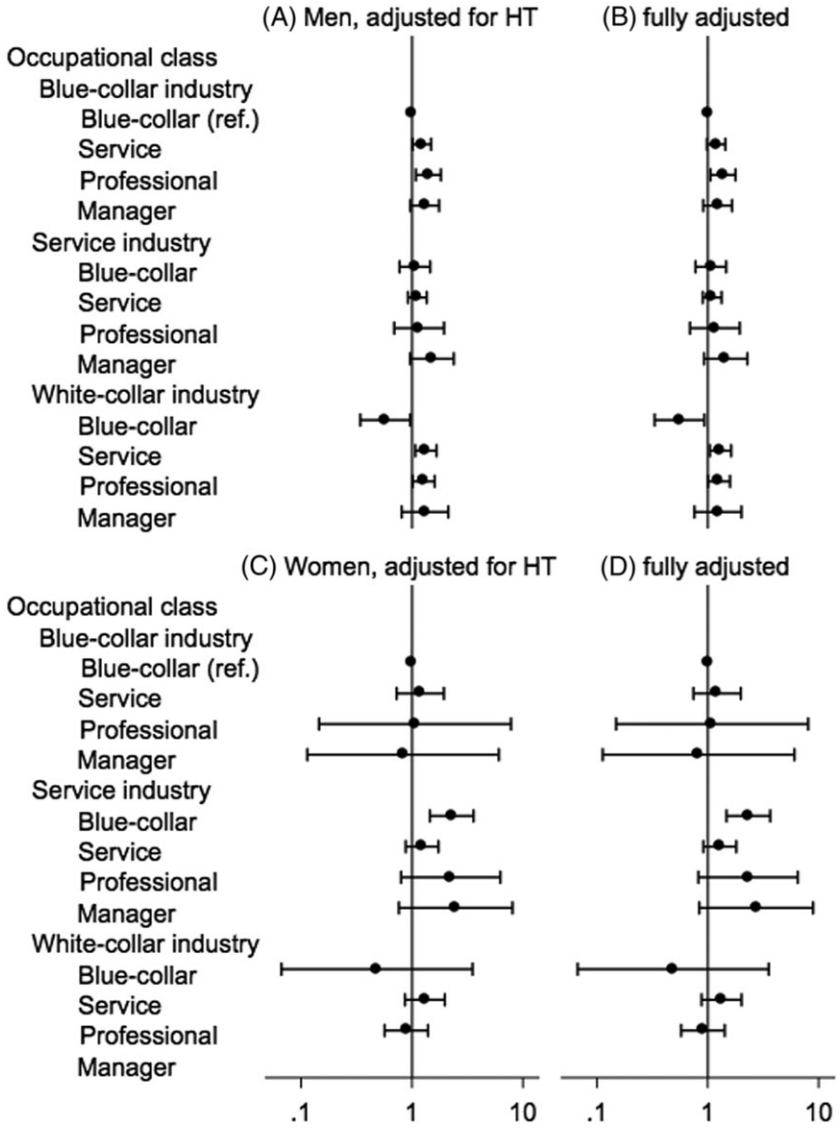

FIGURE 3 Odds ratios adjusted for hypertension and other stress-related factors in a subset data after 2005. The odds ratio (dot) and 95% confidence interval (bar) were estimated by unconditional logistic regression with 5 imputed data. Male and female odds ratios were (A, C) adjusted for age, year of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

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

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

(Continues)

TABLE 2 (Continued)

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

Abbreviation: NA, not available.

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

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

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

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

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

4 | DISCUSSION

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

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

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

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

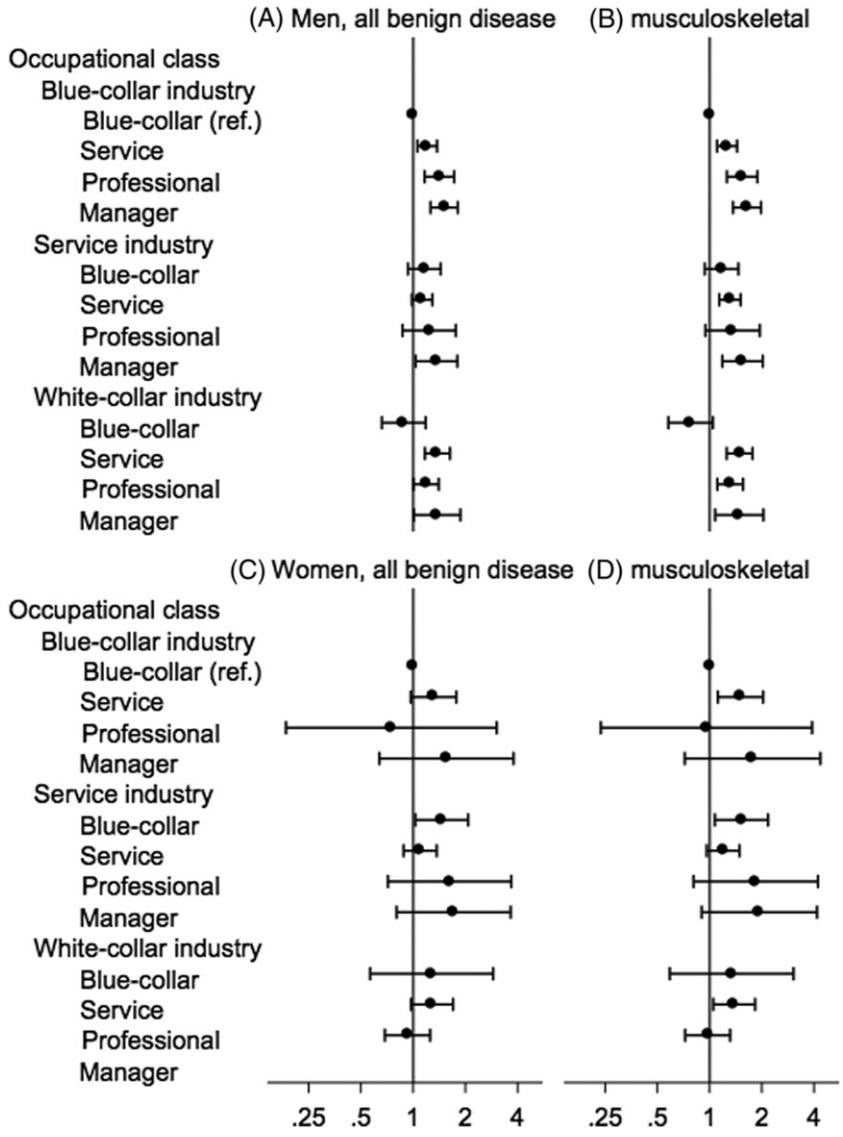

FIGURE 4 Sensitivity analysis with alternative control groups. The odds ratio (dot) and 95% confidence interval (bar) were estimated by unconditional logistic regression, adjusted for age and year of admission with 5 imputed data. Male and female control groups were, respectively, (A, C) patients diagnosed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

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

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

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

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

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

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

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

ETHICS APPROVAL AND INFORMED CONSENT

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

DISCLAIMER

None.

AUTHOR CONTRIBUTIONS

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SUPPORTING INFORMATION

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

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Cholangiocarcinoma Prognosis Varies over Time Depending on Tumor Site and Pathology

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ABSTRACT

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

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

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

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

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

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

INTRODUCTION

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

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

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

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

METHODS

Kanagawa Regional Cancer Registry

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

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

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

Subject and classification method

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

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

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

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

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

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

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

Statistical analysis

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

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

RESULTS

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

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

Table I. Baseline characteristics of cholangiocarcinoma patients

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

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

Three-year survival rate

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

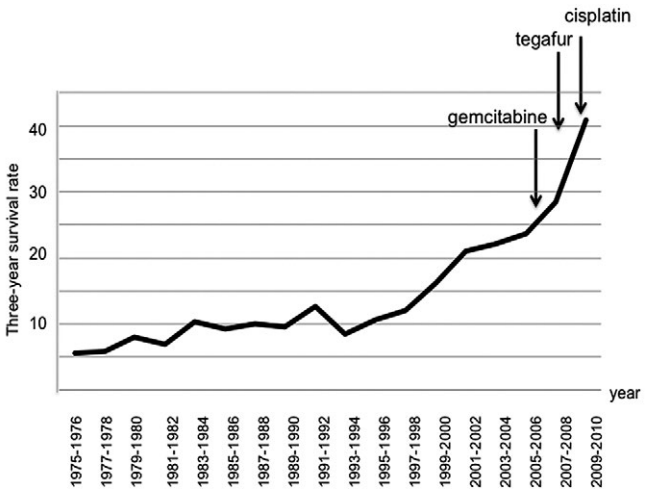

Fig. 1. Three-year survival rates were calculated every two years from 1976 to 2013. Arrows indicate the introduction of gemcitabine, tegafur, and cisplatin treatments.

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

Pathology

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

Table II. Distribution of cholangiocarcinoma with pathological information

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

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

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

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

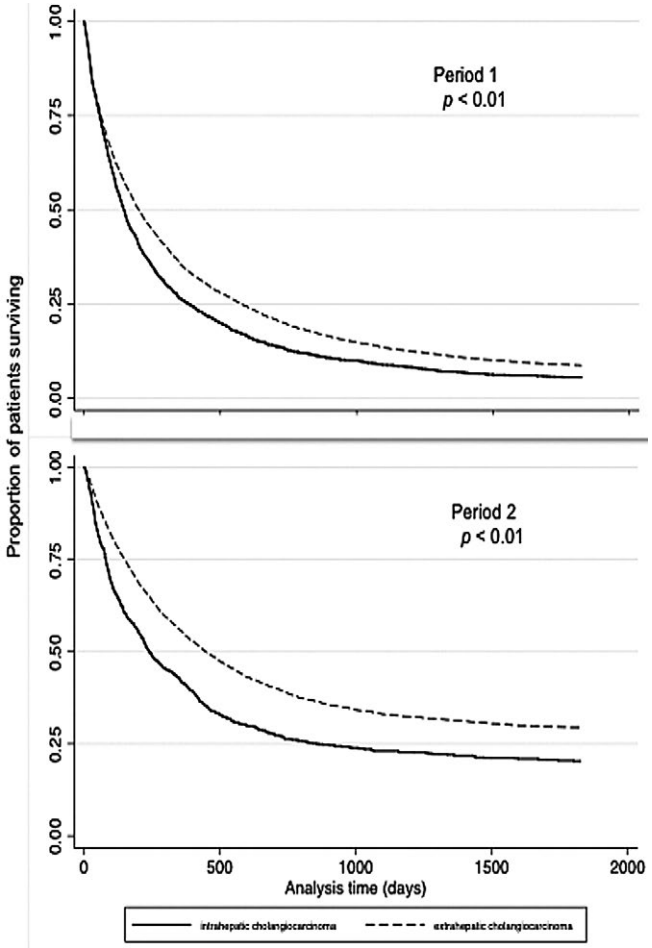

Fig. 2. Kaplan–Meier survival curves for overall survival between intrahepatic and extrahepatic cholangiocarcinoma cases in each period. Survival was estimated using the Kaplan–Meier method in patients with complete information on sex, age, location of bile duct cancer, and observation period, and with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

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

DISCUSSION

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

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

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

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

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

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

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

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

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

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

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

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

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

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

CONCLUSION

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

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

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

Supplementary material: To access the supplementary material visit the online version of the *J Gastrointestin Liver Dis* at http://www.jgld.ro/wp/archive/y2018/n1/a10 and http://dx.doi.org/10.15403/jgld.2014.1121.271.kak

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Supplementary table I. Definition of cholangiocarcinoma pathologies.

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

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

RESEARCH ARTICLE

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

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

Abstract

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

Keywords: liver cancer- hepatocellular carcinoma- survival- epidemiology

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Introduction

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

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

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

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

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

Materials and Methods

Kanagawa Cancer Registry

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

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

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

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

Subjects and classification method

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

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

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

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

Statistical analysis

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

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

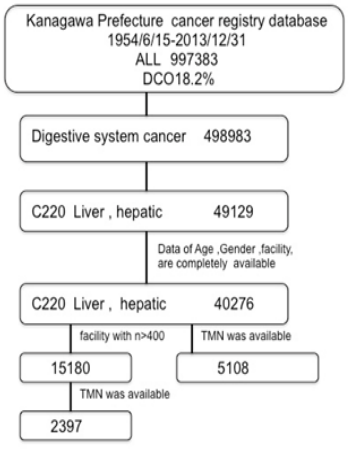

Figure 1. Flow Diagram of Patient Selection Out of a Total of 997,383 Patients (from 1954 to 2013) Identified in the Database of the Kanagawa Cancer Registry, to Reach the Final Number of Eligible Patients Included in This Survival Analysis.

Results

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

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

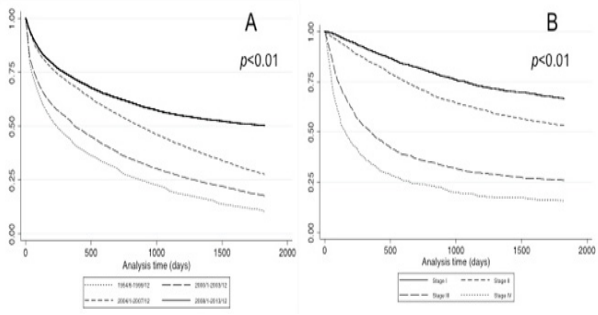

Figure 2. Kaplan–Meier Survival Curves for Overall Survival in Each Period (A) and TNM Stage (B) for Patients with Hepatocellular Carcinoma. Survival was estimated using the Kaplan–Meier method in 31,921 patients with complete information on sex, age and observation period, and with right censoring at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

Table 1. Baseline Characteristics

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

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

Table 2. Distribution of TMN Stage in Each Period

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

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

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

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

Five-year survival rate

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

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

Five-year survival rate in high-volume centers

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

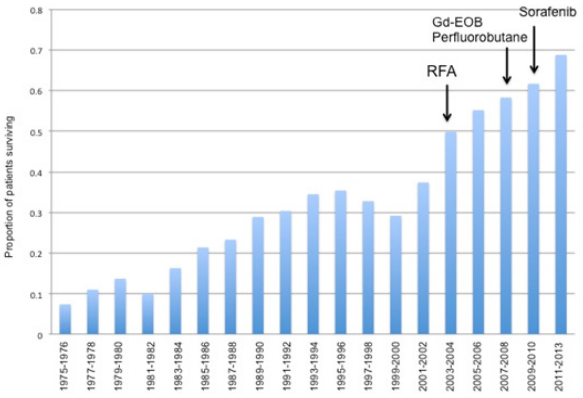

Figure 3. Two-Year Survival Rate Every Two Years from 1975 to 2013. Arrows show the time of radiofrequency ablation, Gd-EOB-DTPA, perfluorobutane and sorafenib introduction. RFA, radiofrequency ablation; Gd-EOB-DTPA, gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid

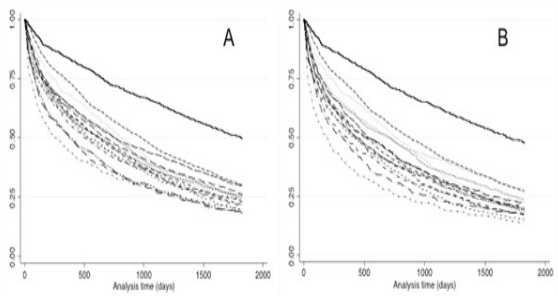

Figure 4. Five-Year Survival Estimated for All High-Volume Centers. Kaplan–Meier survival curves for the overall survival of patients with hepatocellular carcinoma in all cases (A) and those who underwent surgery (B).

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

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

[1]TNM, tumor/node/metastasis classification

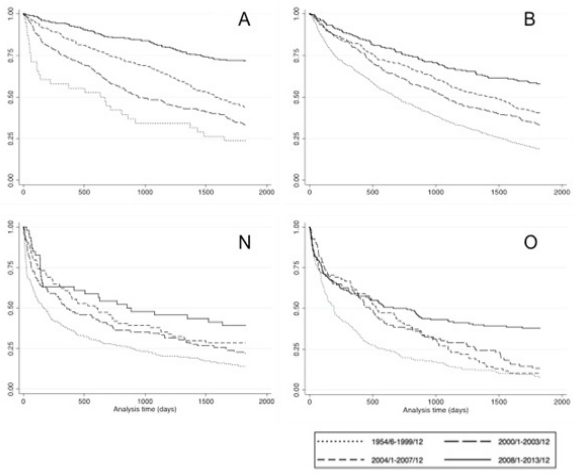

Figure 5. Temporal Change in Five-Year Survival in the Facilities with the Highest Prognosis (A and B), and in Those Two with the Lowest prognosis (N and O). A consistent improvement was obtained in facilities A and B, unlike facilities N and O in which improvement was inconsistent.

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

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

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

Discussion

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

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

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

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

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

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

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

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

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

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

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

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

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Statement conflict of Interest

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

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神 奈 川 の が ん

（神奈川県と全国の経年比較・研究の紹介）

平成30年3月

神奈川県立がんセンター

診断治療技術の進歩が肝臓癌の予後に与えた影響をがん登録から捉える

関東労災病院　消化器内科　　金子　麗奈

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

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

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

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

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

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

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

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

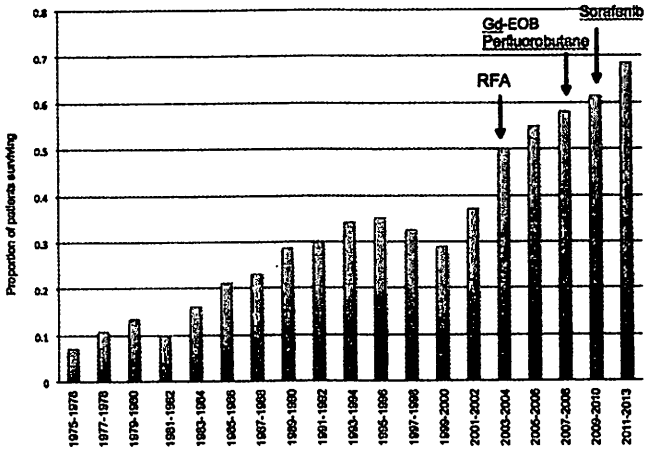

図1　2年ごとの5年生存率

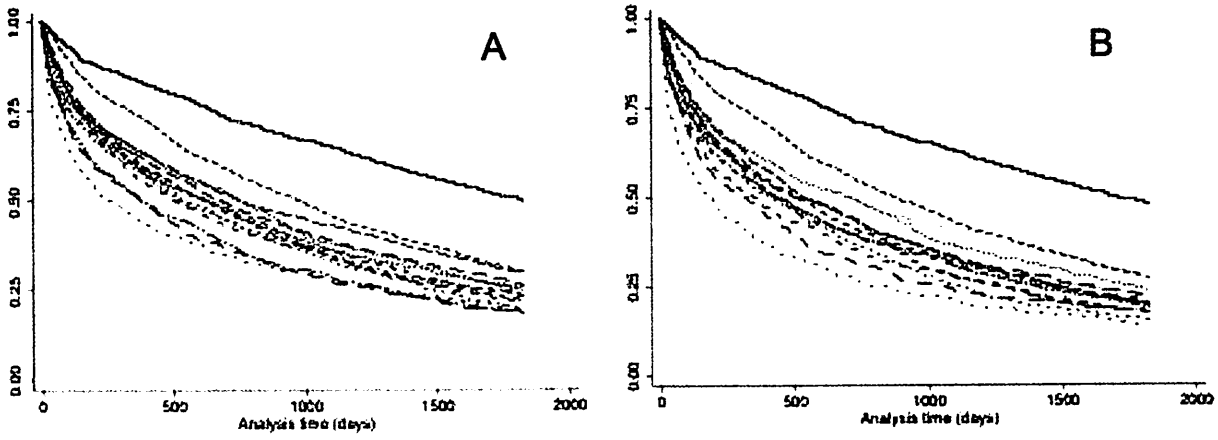

図2　登録数上位施設ごとの5年生存率（A：全症例　B：手術症例）

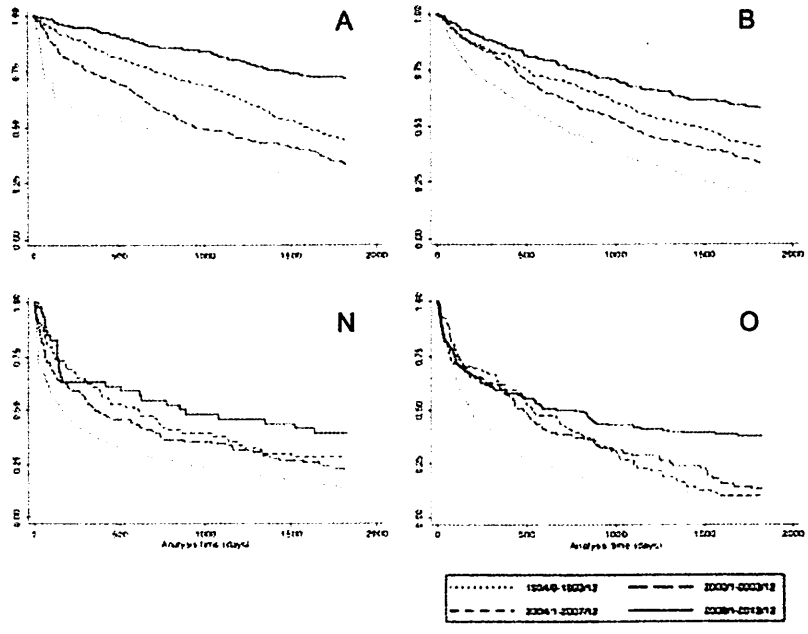

図3 各施設の生存率の経年推移