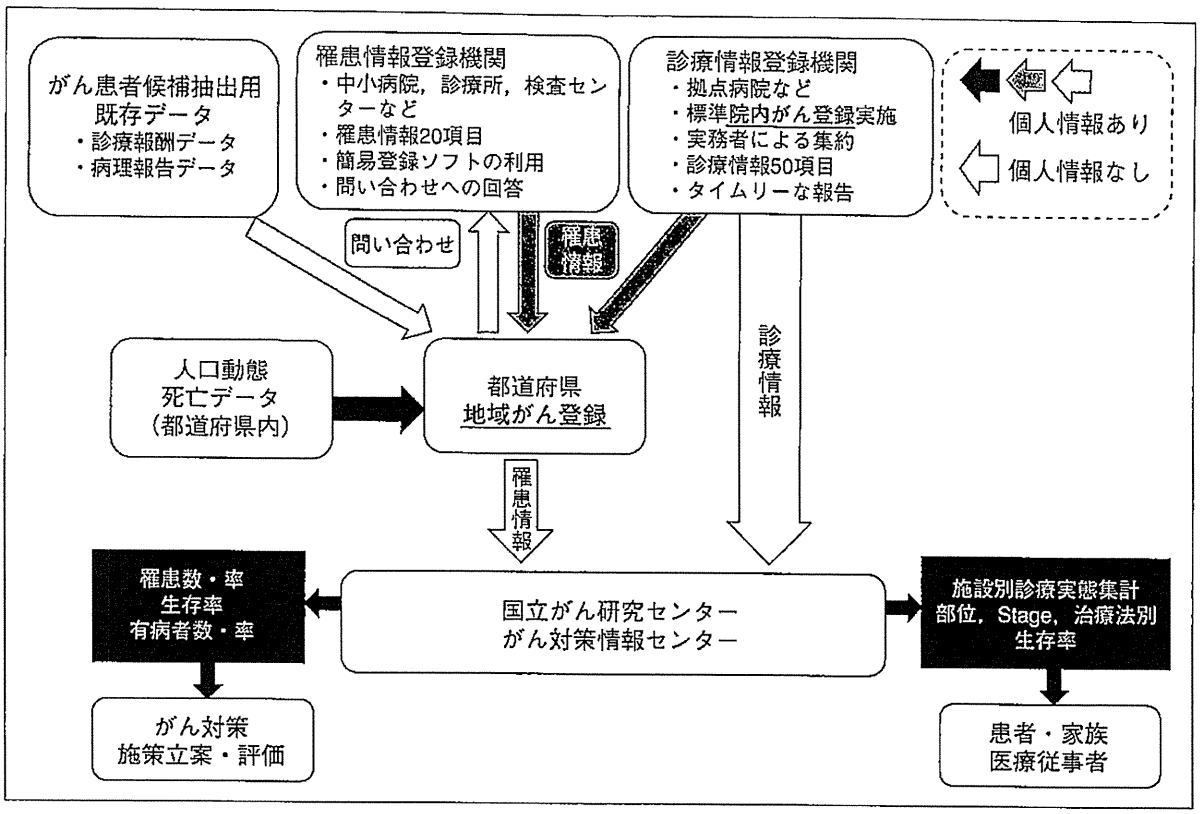

図5　がん登録のデータの流れ(将来案)

・国立がん研究センターがん対策情報センターがん情報サービス．がん診療連携拠点病院向け「院内がん登録」(http://ganjoho.jp/hospital/cancer_registration/index.html)

3．臓器がん登録

臓器がん登録は，学会・研究会が中心となって，会員医師が所属する比較的大きな病院から学会・研究会の中央事務局にデータを集約することにより，全国規模の登録を実施する仕組みである．専門的な医師のいる病院に限られるため，症例に偏りのある危険性があるが，詳細な臨床情報が収集されているため，より適切な進行度分類のあり方の検討，詳細な治療法別の生存率の計測などが可能である．臓器がん登録の横のつながりを保つ仕組みとして，厚生労働省がん研究助成金に臓器がん登録に関する研究班が組織されていたが，現在は，厚生労働省がん研究開発費「院内がん登録および臓器がん登録と連携した診療科データベースの構築と活用に関する研究」に，その役割が引き継がれている．同班が行った18臓器がん登録に対するアンケート調査によると，登録項目数は22～188項目，地域がん登録による全国推定罹患数を分母としたカバー率も6～78%と各登録によってさまざまであった．一方，多くの臓器がん登録でwebか電子媒体を利用し，連結可能匿名化した上でデータ収集を行っていた．生存率を計算するための予後調査の不明割合がいずれの臓器がん登録でも20%前後と高かった．

わが国におけるがん登録の今後の方向性

地域がん登録については，今後実施県の増加が見込まれるとともに，拠点病院からの届出数の増加により，実施県においても精度向上が予想され，全国推計に使用できるがん登録の数は，30道府県(総人口の60%)程度に増加することが期待できる．これまで，厚生労働省研究班を中心に行われてきた標準化，データ収集については，かなり定常化されてきているので，今後は，研究班活動から事業としての活動に移行していくことが考えられる．さらに，登録精度を向上させるためには，法制化(①国の事業，②届出義務，③個人情報を含む既存電子化資料の利用)が

必要と考える．特に，中小病院の届出漏れを確認するためには，レセプトなどの既存電子化資料を利用して，現在の死亡によるさかのぼり調査を前倒しで行うことで，悉皆性を担保し，データ固定の即時性を向上することができる(図5)．

院内がん登録については，拠点病院の登録項目について，必須22項目と標準49項目を整理した上で，地域がん登録との登録項目共通化が必須である．さらに，拠点病院全国集計について，施設別集計の公表を進めることが肝要である．さらに，診療の質評価のため，Quality Indicatorの測定への展開が考えられる．

地域がん登録，院内がん登録，臓器がん登録の3種類のがん登録は，それぞれ目的，実施主体，登録対象，登録項目，収集時期などが異なるため単純に統合することはできないが，共通する部分も多く，相互に連携を深めて，効率の良い登録体制を構築する必要がある．臓器がん登録に対する医療機関側の情報源は各診療科が管理する診療科データベースであることが多いが，患者の基本情報について，院内がん登録とともに病院情報システムから抽出することで省力化が可能である．こうした診療科データベースは，個人情報保護の観点からのシステム管理が徹底されていない場合が多く，院内がん登録や病院情報システムと同レベルのシステム管理の必要性が高まってきている．

一方，多くの地域がん登録は，人口動態統計死亡データおよび住民票照会や本籍地照会による予後調査を実施しているが，これらの情報について院内がん登録を通じて臓器がん登録へ還元することで，医療機関における予後調査の負担を大幅に軽減できる．既存統計資料の有効活用をすることで，予後調査の際のデータ収集を効率的に進めることができる環境を整えることが喫緊の課題である．さらに，がん医療の質の均てん化の程度を検証するためには，適切な対象に対して標準的な診断治療が実施されているかどうかのデータが必要であり，現在の地域・院内がん登録に含まれる項目だけでは，検証は難しく，サンプリング調査やデータベース間の照合などの追加的な調査が必要となる．

2006年10月に，国立がん研究センターにがん対策情報センターが設置され，がん統計・情報部に地域がん登録室と院内がん登録室が設置された．当面，種々の研究班と連携しながら，地域がん登録と院内がん登録の標準化と体制整備を支援するとともに，実務担当者の教育研修を行うことが想定されているが，今後は，種々のがん関連の統計を一元的に収集整理して，正確で役に立つがん統計情報の提供を進め，データ利用をより一層進めていく必要がある．

*　　*　　*

呼吸器内科，19(4)：287-292，2011

特集 パラダイムシフトを迎えた肺がん治療

疫学からみた日本における肺がんの動向*

雑賀 公美子**
祖父江 友孝**

Key Words : lung cancer mortality, lung cancer incidence, risk facto

死亡数・死亡率の年次推移

2009年の厚生労働省の人口動態調査死亡統計によると，肺がん死亡数は，男性の全がん死亡の23.8％を占める49,035人(第１位)，女性の全がん死亡の13.5％を占める18,548人(第２位)であり，最も頻度の高いがんの１つである．

肺がん粗死亡率の年次推移は，男性では1960年に7.9(人口10万対)であったのが，以降急速に増加し，1993年には胃がんを抜いて第１位となった．女性では1960年に粗死亡率が3.2(人口10万対)であったのが，1960年から2009年まで一貫して増加し，1980年には胃がん，大腸がんに次いで第３位となり，2007年には胃がんを抜いて第２位となった．2009年の粗死亡率は，男性では79.9(人口10万対)，女性では28.8である．年齢階級別の近年の増減の傾向は年齢階級によって異なる．1960年以降，特に70歳以上の男女の死亡率の増加は著しく，70歳代の男女および80～84歳の女性においては近年減少傾向を示しているが，80歳以上の男性および85歳以上の女性は増加傾向を続けている(図１)．

粗死亡率は，高齢化などの年齢分布の影響を大きく受けるため，その影響を除いた年齢調整死亡率(基準人口は昭和60年モデル人口)をみると，男女とも1960年代～1980年代に急激に増加したが，1990年代後半から減少傾向を示している．2009年の年齢調整死亡率は，男性で42.5(人口10万対)，女性で11.4であった．

罹患数・罹患率の年次推移

がんの罹患に関しての情報は，地域がん登録のデータから推計されている．肺がん罹患数は，2005年の男性の全がん罹患の15.4％を占める58,264人(第３位)，女性の全がん死亡の9.6％を占める25,617人(第４位)である．

肺がん粗罹患率の年次推移をみると，1975年には男性で23.1(人口10万対)，女性で8.7であったが，男女ともに増加し，2005年には男性93.4(人口10万対)，女性39.2となった．また，年齢階級別の年次推移をみると，男性の増減傾向は死亡と類似しており，70歳以上の著しい罹患率の増加および65～74歳での近年の減少傾向が観察された．女性は，死亡の年次推移とは異なり，すべての年齢階級において1975年以降増加傾向を続けている(図２)．

年齢調整罹患率(基準人口は昭和60年モデル人口)は，男性は1975～1990年まで増加し，1990年代は横ばい，2005年には58.5(人口10万対)となっている．女性は1975年以降緩やかな増加傾向が続いており，2005年の年齢調整罹患率は20.2であった．

* Epidemiology in lung cancer.

** Kumiko SAIKA, Ph.D. & Tomotaka SOBUE, M.D.: 国立がんセンターがん対策情報センターがん統計研究部〔〒104-0045 東京都中央区築地5-1-1〕; Surveillance Division, Center for Cancer Control and Information Services, Tokyo 104-0045, JAPAN

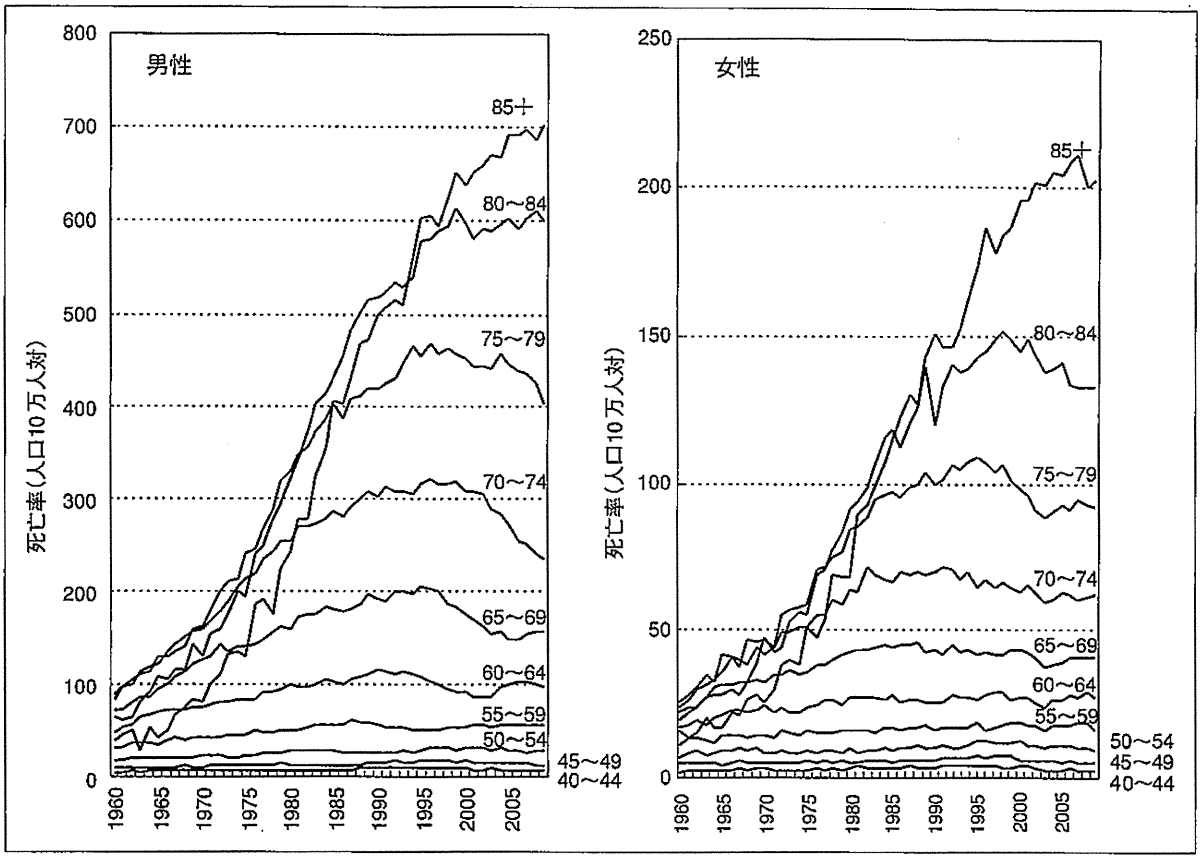

図1　年齢階級別肺がん死亡率の年次推移（1960～2009年）（文献[14]より引用改変）

死亡と罹患の比較

1975～2005年の肺がんの粗死亡率と粗罹患率を比べると，男性では近年の40歳代および50歳代で罹患が死亡の1.5倍以上であるものの，60歳以上の年齢階級では，1.0～1.5倍でほぼ平行に推移している．一方，女性では80歳以上の高齢者では罹患は死亡の1.0～1.2倍で平行に推移しているが，80歳未満では1990年以降は死亡率の1.2～2.0倍となり，死亡と罹患との間に若干の乖離が認められる．特に40歳代および50歳代における2003年以降の罹患と死亡の乖離は著しい．

性・年齢階級別年次推移

年齢階級別の肺がん死亡数は，男女とも40歳以上から増加し始め，男性では75歳以上80歳未満で最も多く，女性では，年齢が高いほど死亡数は多い．死亡率は，男女とも年齢が高いほど高くなっている（図3）．肺がん死亡者全体に占める75歳以上の者の割合は，年々増加しており，1960年では男性11.9%，女性15.0%であったのが，2005年には，男性55.1%，女性63.3%となり，半数以上を占めている．

年齢階級別の肺がん罹患数は，男女とも死亡より少し若い35歳以上から増加し始め，男性では75歳以上80歳未満，女性では85歳以上の罹患数が最も多い．罹患率においては，男女とも年齢が高いほど高くなっている（図4）．死亡と同様に肺がん罹患者全体に占める75歳以上の者の割合は年々増加しており，1975年では男性22.5%，女性25.8%であったのが，2005年には，男性45.1%，女性46.7%にまで増加している．

生存率

地域がん登録のデータから推計された肺がんの5年相対生存率は，1993～1996年に診断された患者では，男性20.8%，女性27.1%であり，1997～1999年に診断された患者では，男性22.4%，女性33.5%と，男女ともに増加している[1]．

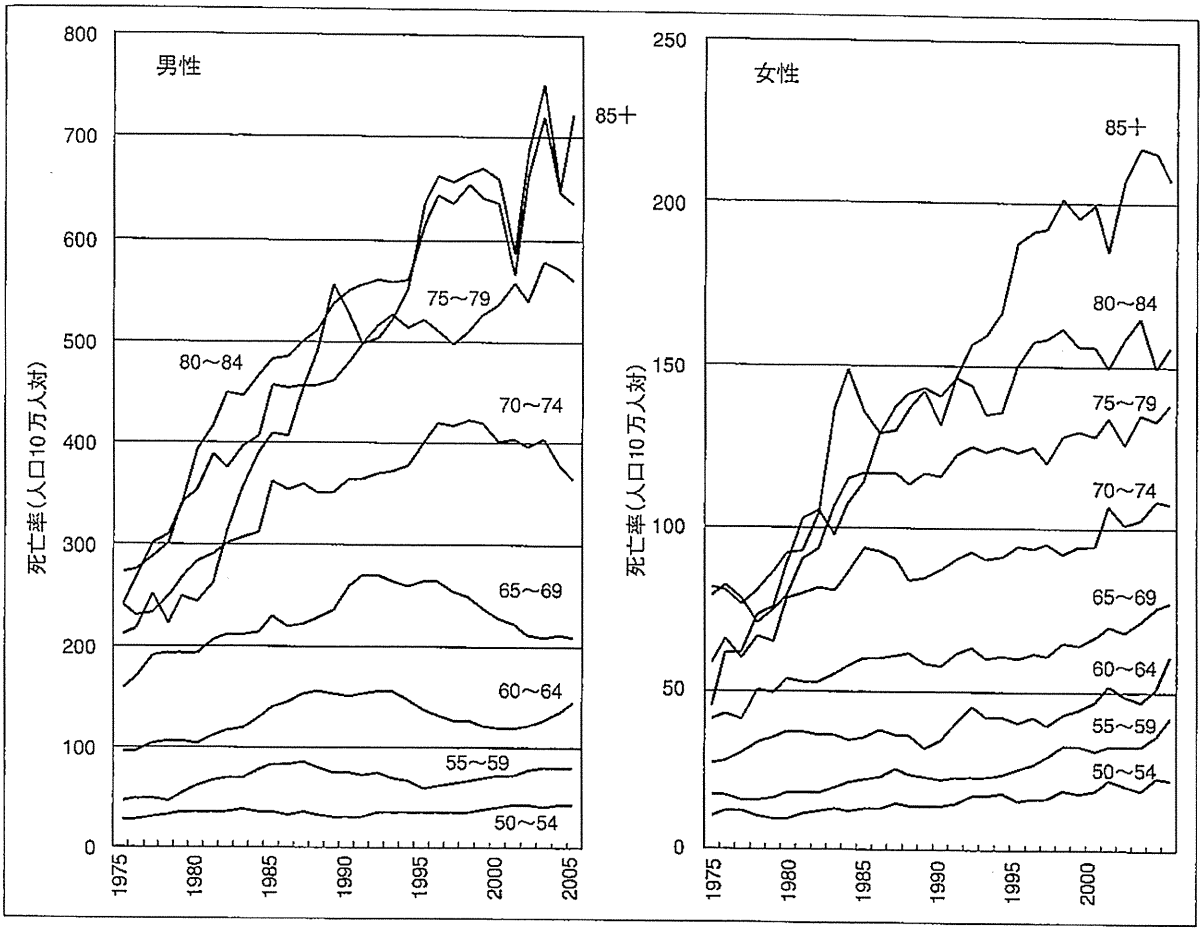

図２　年齢階級別肺がん罹患率の年次推移（1975～2005年）（文献[15]より引用改変）

組織型別割合

大阪府がん登録データから，1975年～2003年までの組織型別の割合を６期間に分けて傾向をみると，男性では1993年までは扁平上皮がんが最も多かったのが，腺がんの割合が増加し，1994年以降は腺がんが最も多くなった．女性は，観察期間を通して腺がんが最も多く，1975～1978年の61%から増加傾向である[2]．最新の1999～2003年の肺がん罹患においては腺がんが，男性肺がんの43%，女性肺がんの67%を占めている．そのほか，扁平上皮がんは男性肺がんの35%，女性肺がんの16%を占め，小細胞肺がんが男性肺がんの16%，女性肺がんの12%を占めている[2]．

危険因子

１．喫　煙

喫煙は肺がんの危険因子の中で，最も影響が大きい．非喫煙者に対する喫煙者の肺がんリスクは，日本人を対象とした疫学研究より，男性で4.4倍，女性で2.8倍と報告されている[3]．組織型別では，扁平上皮がんと小細胞がんが喫煙との関連が強く，腺がんとの関連は弱い．受動喫煙も危険因子であり，夫が喫煙している非喫煙者の妻の肺がんのリスクは，夫が喫煙していない妻に比べて1.3倍高い[4]．職場での受動喫煙においても，職場で喫煙に曝露している集団は，肺がんのリスクが1.3倍高いと報告されている[4]．国内での代表的なコホート研究のデータを併合した日本人における喫煙による負荷を推計した研究によると，男性では肺がんの69.2%，女性では18.9%が喫煙に起因するものであると推計された[5]．

２．職場および家庭における危険因子

世界保健機構（WHO）によると，家庭内でのラドンへの曝露は肺がんの２番目に影響の大きい危険因子であり，肺がんの３～14%はラドンによるものであると推計されている[6]．そのほか，国際がん研究機関（IARC）が発がん物質としてあげ

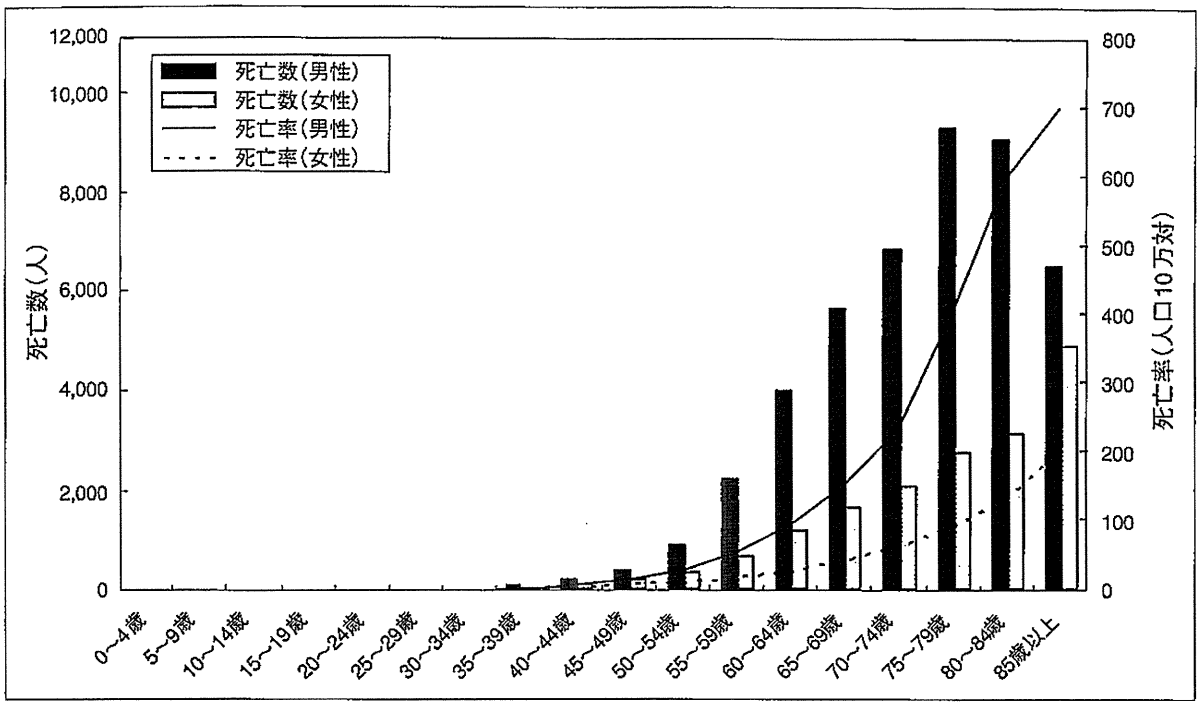

図3　年齢階級別肺がん死亡数・死亡率(2009年)(文献[14]より引用改変)

ている，職場で曝露する可能性のある肺がんの危険因子には，アルミニウム，アスベスト，ヒ素，シリカ，クロロメチルエーテルなどがある[7]．

大気汚染においては，わが国では1970年以降，工場から排出されるSO2などの汚染状況は改善したが，自動車からのNO2，排気ガスに含まれる黒煙粒子などの状況は改善されていない．大気中の約3,000の明らかになっている化学物質のうち，10%に発がん可能性があり，多くが動物実験にて発がん性があるとされている[8]．大気汚染の著しい地域では，大気中に多環芳香族炭化水素，重金属，アスベストなどが含まれていることから大気汚染と肺がんの関係が検討されている．特に最近は，粒径の細かい(2.5ミクロン以下)微小粒子と肺がんとの関係が注目されている[9]．

3. 食 習 慣

食物とがんに関する国際的な評価は，約7,000件の文献を系統的にレビューした世界がん研究基金による報告書がある．この報告書では，要因とがんとの関連について科学的根拠としての信頼性を「確実」，「ほぼ確実」，「限定的―示唆的」，「限定的―判定不能」，「リスクへの明らかな影響の可能性が低い」の5段階で評価している．肺がんリスクを低下させるものとして「ほぼ確実」なのは果物とカロテノイドを含む食品であり，リスクを上昇させるものとして「確実」なのは飲料水中のヒ素とβ-カロテンサプリメントであった．「限定的―示唆的」とされたものでは，肺がんのリスク低下について，でんぷん質ではない野菜，セレニウムを含む食品，ケルセチンを含む食品，セレニウムであり，リスク上昇については，赤身肉，加工肉(燻製，塩漬あるいは保存料を添加した肉)，脂肪，バター，レチノールサプリメントがあった．

日本人の生活習慣におけるがん危険因子の総合的な評価は，「生活習慣病によるがん予防法の開発と評価」研究班(主任研究者：津金昌一郎)において行われており，日本人を対象に主要な危険要因とがんとの関連を調べた疫学研究について科学的根拠としての信頼性に関する総合評価を行い，ホームページで情報を公開している(http://epi.ncc.go.jp/can_prev/)．この評価は，収集した文献から個々の疫学研究についての危険因子とがんとの関連の強さを確認し，さらに動物モデルやメカニズムなど疫学研究以外からの科学的根拠を考慮しながら行われている．科学的根拠としての信頼性の評価は，「確実」，「ほぼ確実」，「可能性あり」，「十分でない」の4段

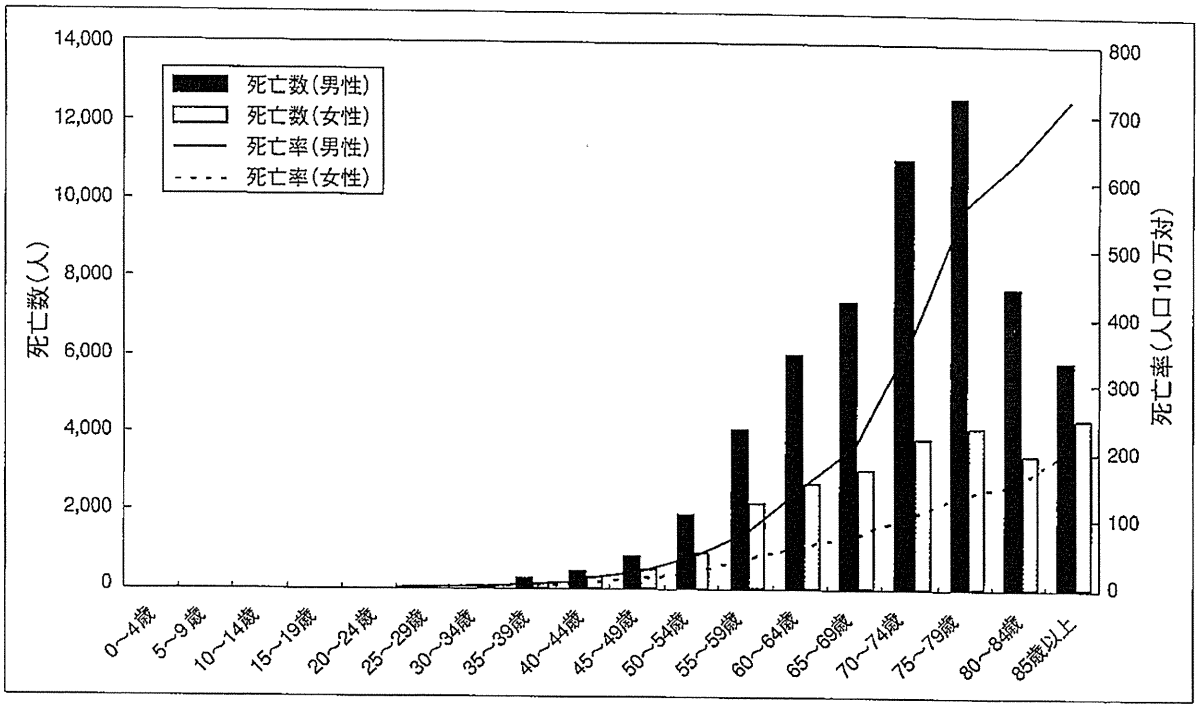

図4　年齢階級別肺がん罹患数・罹患率(2005年)(文献[15]より引用改変)

階にランク分けされている．肺がんについては，リスクを低下または上昇させるものとして「確実」または「ほぼ確実」な食品はなく，果物だけがリスク低下において「可能性あり」としてあげられている．

(1)ヒ素

動物実験において，飲料水中のヒ素と肺がんの発がんとの関係は明らかにされており，疫学研究においても飲料水中のヒ素が肺がんおよび慢性肺疾患のリスクを上げることが証明されている．

(2)カロテノイド

従来の観察的な研究では，血中β-カロテンの濃度が低い人には肺がんが発症しやすく，その差は非喫煙者よりも喫煙者の方が大きいとされていた．また，肺がんとさまざまなカロテノイドの関係をみた研究によると，リコピン，ルテイン/ゼアキサンチン，β-クリプトキサンチン，総カロテノイド，血清β-カロテン，血清レチノールの摂取量が最も多い集団は最も少ない集団よりも肺がんのリスクが低いと報告されていた．しかし，その後の欧米での介入研究の結果では，喫煙者に対してβ-カロテンサプリメントの投与群で肺がんが増加したとの報告がある．

(3)果物

従来の欧米の研究では，肺がんのリスクを下げる可能性があるとされていたが，最近の欧米の研究や日本人を対象とした大規模コホート調査では，野菜・果物の摂取で肺がんのリスクは下がらないという結果が報告されており[11]，証拠は十分ではない．米国がん研究協会(AICR)の報告によると果物については，機序は明らかではないが，予防的な効果のある可能性が高いとされている[10]．

予防対策

1．1次予防

男性では肺がんの69.2%，女性では18.9%が喫煙に起因するものであることから[5]，肺がんの1次予防には，喫煙対策を中心に実施すべきことは明白である．

国民健康・栄養調査によると，わが国における現在喫煙者率は，2009年において，男性で38.2%，女性で10.9%であり[12]，男性は減少してきているものの，欧米と比較すると，約2倍と高い．また，女性は増加傾向にあり，1990年代前半までは欧米の半分であった喫煙率が2/3まで増加している．最近では，男性喫煙率は全年

齢階級において減少傾向にあるが，女性では20代，30代の若い世代での喫煙率増加が顕著であることから，これらの対象を中心とした一層の喫煙対策の強化が必要である．

2．2次予防

わが国では1987年以降老人保健法に基づく老人保健事業として肺がん検診を実施していたが，1998年以降は一般財源化された．国が「がん予防重点健康教育およびがん検診実施のための指針」で示した標準的な肺がん検診は，40歳以上を対象とした胸部X線検査と重喫煙者などのリスクの高い集団への喀痰細胞診であり[13]，死亡率減少効果について相応の証拠があると判断されている．

肺がんの死亡率と罹患率の差は，肺がんの早期発見，早期治療の効果の評価指標と考えられるため，死亡率と罹患率の年次推移を比較すると，60歳以上の男性については乖離がほとんど観察されず，国レベルの対策として効果が示されていない．しかし，40歳代，50歳代の男性および女性については，若干の乖離が観察されており，対策の効果の可能性があるが，治療方法の改善や過剰診断などの可能性もある．

文　献

1) Matsuda T, Ajiki W, Marugame T, et al. Population-based survival of cancer patients diagnosed between 1993 and 1999 in Japan : A chronological and international comparison study. Jpn J Clin Oncol 2011 ; 41 : 40.
2) Toyoda Y, Nakayama T, Ioka A, et al. Trends in lung cancer incidence by histological type in Osaka, Japan. Jpn J Clin Oncol 2008 ; 38 : 534.
3) Wakai K, Inoue M, Tanaka K, et al. Tobacco smoking and lung cancer risk : An evaluation based on a systematic review of epidemiological evidence among the Japanese population. Jpn J Clin Oncol 2006 ; 36 : 309.
4) Kurahashi N, Inoue M, Liu Y, et al. Passive smoking and in Japanese non-smoking women : A prospective study. Int J Cancer 2008 ; 122 : 653.
5) Katanoda K, Marugame T, Saika K, et al. Population attributable fraction of mortality associated with tobacco smoking in Japan : A pooled analysis of three large-scale cohort studies. J Epidemiol 2008 ; 18 : 251.
6) World Health Organization. WHO handbook on indoor radon : A public perspective. Geneva : WHO Press ; 2009. p. 3.
7) World Health Organization, International Agency for Research on Cancer. IARC monographs on the evaluation of carcinogenic risks to humans. Lyon : IARC Press ; 1972-2010. Vol. 1-99.
8) Lewtas J. Experimental evidence for the carcinogenicity of air pollutants. In : Tomatis L, editors. Air Pollution and Human Cancer. Berlin : Springer-Verlag ; 1990. p. 49.
9) Pope CA III, Burnett RT, Thun MJ, et al. Lung cancer, cardiopulmonary mortality, and long-term exposure to fine particulate air pollution. JAMA 2002 ; 287 : 1132.
10) World Cancer Research Fund / American Institute for Cancer Research. Food, Nutrition, Physical Activity, and the Prevention of Cancer : a Global Perspective. Washington DC : AICR ; 2007. p. 259.
11) Liu Y, Sobue T, Otani T, Tsugane S. Vegetables, fruit consumption and risk of lung cancer among middle-aged Japanese men and women ; JPHC study. Cancer Causes and Control 2004 ; 15 : 349.
12) 厚生労働省健康局総務課生活習慣病対策室．平成21年国民健康・栄養調査結果の概要．2009．p. 28.
13) 祖父江友孝．有効性評価に基づく肺がん検診ガイドライン．平成18年度厚生労働省がん研究助成金「がん検診の適切な方法とその評価法の確立に関する研究」班．2006.
14) 厚生労働省大臣官房統計情報部．人口動態統計．国立がん研究センターがん対策情報センター．Available from : URL : http://ganjoho.ncc.go.jp/professional/statistics/statistics.html
15) 地域がん登録研究班．地域がん登録全国推計値．国立がん研究センターがん対策情報センター．Available from : URL : http://ganjoho.ncc.go.jp/professional/statistics/statistics.html

World Journal of Gastroenterology

Online Submissions: http://www.wjgnet.com/1007-9327office
wjg@wjgnet.com
doi:10.3748/wjg.v17.i39.4421

World J Gastroenterol 2011 October 21; 17(39): 4421-4428
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

BRIEF ARTICLE

Comparative epidemiology of gastric cancer between Japan and China

Yingsong Lin, Junko Ueda, Shogo Kikuchi, Yukari Totsuka, Wen-Qiang Wei, You-Lin Qiao, Manami Inoue

Yingsong Lin, Junko Ueda, Shogo Kikuchi, Department of Public Health, Aichi Medical University School of Medicine, Aichi 480-1195, Japan
Yukari Totsuka, Division of Cancer Development System, National Cancer Center Research Institute, Tokyo 104-0045, Japan
Wen-Qiang Wei, You-Lin Qiao, Department of Cancer Epidemiology, Cancer Institute/Hospital, Chinese Academy of Medical Sciences, Beijing 100730, China
Manami Inoue, Epidemiology and Prevention Division, Research Center for Cancer Prevention and Screening, National Cancer Center Research Institute, Tokyo 104-0045, Japan
Author contributions: Lin Y, Totsuka Y, and Inoue M contributed to the conception of this review article; Lin Y and Ueda J performed the literature research; Lin Y drafted the article; Totsuka Y, Kikuchi S, Wei WQ, Qiao YL, and Inoue M provided valuable comments and revised the article.
Supported by Grant-in-Aid from the Third Term Comprehensive Control Research for Cancer, the Ministry of Health, Labour and Welfare, Japan
Correspondence to: Yingsong Lin, MD, PhD, Department of Public Health, Aichi Medical University School of Medicine, 21 Yazako, Karimata, Nagakute-cho, Aichi 480-1195, Japan. linys@aichi-med-u.ac.jp
Telephone: +81-561-623311 Fax: +81-561-625270
Received: February 21, 2011 Revised: June 9, 2011
Accepted: June 16, 2011
Published online: October 21, 2011

Abstract

AIM: To clarify the similarities and differences in gastric cancer epidemiology between Japan and China.

METHODS: A comprehensive literature search of the PubMed database was performed. The relevant literature published in China was also been cited. Data on incidence and mortality rates in 2008 were obtained from the Cancer Mondial database, published by International Agency for Research on Cancer at http://www-dep.iarc.fr/.

RESULTS: Gastric cancer remains a significant public health burden in both Japan and China. The prevalence of *Helicobacter pylori* (*H. pylori*) colonization is high in the adult populations of both countries. Accumulating evidence from intervention studies in both countries has shown the effectiveness of *H. pylori* eradication in reducing gastric cancer incidence. There are differences, however, in many aspects of gastric cancer, including patterns of incidence and mortality, trends in the prevalence of *H. pylori* infection, *H. pylori* strains, the magnitude of risk of gastric cancer related to *H. pylori* infection, and associations with dietary habits. Compared with China, Japan has seen a more rapid decline in *H. pylori* infection among adolescents. While Japanese cohort studies have dominated the literature concerning the associations between gastric cancer and dietary habits, numerous case-control studies in China suggest a positive association between a high intake of preserved fish and vegetables and gastric cancer risk. There is a need for a multidisciplinary research approach to understand the interactions between various strains of *H. pylori*, host factors, and other lifestyle and environmental factors in gastric carcinogenesis in both countries.

CONCLUSION: The shared high incidence of gastric cancer and high prevalence of *H. pylori*, as well as differences in many aspects of gastric cancer, provide an excellent opportunity to establish Sino-Japanese collaborations.

Key words: Gastric cancer; Risk factor; *Helicobacter pylori*; Epidemiology

Peer reviewers: David J McGee, PhD, Associate Professor, Department of Microbiology and Immunology, Louisiana State University Health Sciences Center-Shreveport, 1501 Kings Highway, Shreveport, LA 71130, United States; Hikaru Nagahara, Professor, Department of Gastroenterology, Aoyama Hospital, Tokyo Women's Medical University, 2-7-13 Kitaaoyama Minato-ku, Tokyo 107-0061, Japan

Lin Y, Ueda J, Kikuchi S, Totsuka Y, Wei WQ, Qiao YL, Inoue M. Comparative epidemiology of gastric cancer between Japan and China. *World J Gastroenterol* 2011; 17(39): 4421-4428 Available from: URL: http://www.wjgnet.com/1007-9327/full/v17/i39/4421.htm DOI: http://dx.doi.org/10.3748/wjg.v17.i39.4421

INTRODUCTION

Gastric cancer is a heterogeneous, multifactorial disease. The incidence and mortality vary geographically, with the highest rates in East Asia (Japan, China and Korea)[1]. Although a trend of declining incidence has been observed in Japan and China, gastric cancer still represents a tremendous burden in each country. According to the vital statistics released by the Ministry of Health, Welfare and Labor in Japan, approximately 50 000 Japanese men and women die from gastric cancer annually, representing approximately 15% of annual cancer-related deaths over the past four decades[2]. No systematic national vital statistics exist in China, but a retrospective sampling survey on malignant tumors from 2004 to 2005 found that the mortality rate from gastric cancer ranked third in overall cancer mortality[3]. Notably, China alone accounts for 42% of all gastric cancer cases worldwide, at least in part because of its large population[1].

Numerous epidemiologic studies have been conducted in Japan and China to identify environmental and lifestyle factors that contribute to the development of gastric cancer; these studies have identified *Helicobacter pylori* (*H. pylori*) infection as an important risk factor for gastric cancer[4]. Additionally, high salt intake and exposure to *N*-nitroso compounds significantly increase the risk among *H. pylori* infected individuals[5]. It is noteworthy that Japan has a strong tradition of gastric cancer research, not only in basic science but also in epidemiology and clinical trials. Seminal papers published during the last three decades have greatly contributed to our understanding of gastric cancer etiology and prevention[6-9]. However, an increasing number of case-control studies in different regions of China have examined risk factors for gastric cancer, and cohort studies are ongoing to investigate the role of lifestyle in urban and rural areas[10-12].

In this article, we first summarize the current understanding of gastric cancer etiology on the basis of existing literature. We then compare the burden of gastric cancer between Japan and China in terms of trends in incidence and mortality. Next, we address three of the principal risk factors, based on epidemiologic studies conducted in each country: *H. pylori* infection, cigarette smoking and diet. Finally, we propose three potential avenues for Sino-Japanese collaboration.

MATERIALS AND METHODS

We performed a comprehensive literature search of the PubMed database using the search terms "risk factors", "*H. pylori*", "smoking", "diet", "gastric cancer", "China", and "Japan". In addition, relevant literature published in China was also cited. Data on incidence and mortality in 2008 were obtained from the Cancer Mondial database, published by International Agency for Research on Cancer (IARC) at http://www-dep.iarc.fr/.

RESULTS

Current knowledge about gastric carcinogenesis

Gastric cancer is a multifactorial disease with a complex interplay between genetics and both lifestyle and environmental factors. Gastric cancer can be classified as intestinal or diffuse. While the triggering factor and the histopathologic changes in the progression of diffuse gastric cancer remain incompletely understood, the progression of intestinal gastric cancer is well characterized[13]. An individual develops intestinal cancer through a series of histological changes beginning with the transition from normal mucosa to chronic superficial gastritis, which then leads to atrophic gastritis, intestinal metaplasia, and finally dysplasia and adenocarcinoma[13]. Before the discovery of *H. pylori* in 1983, epidemiologic studies had already suggested an important role for lifestyle in the etiology of gastric cancer. In particular, a high-salt diet and foods rich in *N*-nitroso compounds appeared to be major inducers of gastric cancer. Since the discovery of *H. pylori,* its close association with peptic ulcers and gastric cancer has been supported by numerous studies. Asia-Pacific consensus guidelines on gastric cancer prevention define *H. pylori* infection as necessary but not sufficient for the development of non-cardia gastric adenocarcinoma[4]. From an epidemiologic perspective, the synergistic interaction between *H. pylori* and diet plays an overriding role in gastric carcinogenesis[14].

However, current studies have not provided a clear answer as to why only a minority of individuals with *H. pylori* infection develop gastric cancer. One reason is that the interactions of *H. pylori* strains, host factors, and other lifestyle and environmental factors in gastric carcinogenesis are not well defined. Another reason is that few causally linked genes have been found, and the role of genetic and epigenetic changes in gastric carcinogenesis is poorly understood. These two issues need to be addressed in future studies.

Descriptive epidemiology of gastric cancer in Japan and China

Patterns of gastric cancer incidence, mortality and trends: According to Globocan 2008, gastric cancer is the third most frequently diagnosed cancer and the second leading cause of cancer deaths in Japan, with an estimated 102 040 new cases and 50 156 cancer deaths in 2008. The overall estimated age-adjusted incidence rate (standardized for world population) in 2008 was 31.1 per 100 000 people. However, gastric cancer is the second most frequently diagnosed cancer and the third lead-

Table 1 Comparisons of crude and age-standardized incidence rates of gastric cancer between Japan and China (1993-1997)

	Men		Women	
	Crude	ASR	Crude	ASR
Japan				
Hiroshima	113.1	85.5	55.1	33.9
Miyagi	109.2	69	52.2	27.1
Nagasaki	119.9	65.4	56.5	25.6
Osaka	87.7	59.9	42.9	23.8
Saga	115.8	63.6	57	24.9
Yamagata	178.5	91.6	94.1	38.9
China				
Beijing	27.8	19.8	13	8.7
Changle	103.5	145	29.6	34.5
Cixian	55.9	78.1	28	31.9
Jiashan	45.8	38.9	20.3	15.7
Qidong	39.5	37.8	24.2	19
Shanghai	54.6	32.3	29.8	17.6
Tianjin	33.5	26.9	13.9	10
Wuhan	29.3	29.8	17.1	14.5

Source: Cancer incidence in five continents Vol. Ⅷ, IARC scientific publications No. 155. ASR: Age standardized rate, per 100 000 population.

ing cause of cancer death in China, with an estimated 464 439 new cases and 352 315 cancer deaths in 2008. The overall estimated age-adjusted incidence rate in 2008 was 29.9 per 100 000 people in China.

Although China's overall incidence rate is comparable to that of Japan, a wider variation in both crude and age-standardized rates is apparent when cancer registry data (1993-1997) from the 2 countries are compared (Table 1). For example, the incidence in Changle was 145 per 100 000 people, approximately 7 times higher than in Beijing. The highest rates were often found in economically undeveloped rural areas in China, including Gansu, Henan, Hebei, Shanxi, and Shaanxi Provinces[15]. Although gastric cancer incidence is declining in both rural and urban areas in China[16-18], the rate of decline may be slower than in developed countries[19]. The number of new gastric cancer cases has been projected to increase continuously over the next 40 years because of population growth and aging[19].

Risk factors for gastric cancer in Japan and China

From the large body of literature on gastric cancer etiology in Japan and China, we cite selected epidemiologic studies conducted in each country. Three major risk factors, namely *H. pylori* infection, cigarette smoking and high intake of salt/salty food, are addressed in detail.

H. pylori colonization: Prevalence of H. pylori colonization in the general population

Japan: Gastric *H. pylori* infection is common among middle-aged and elderly Japanese people. A seroepidemiological study of *H. pylori* infection among apparently healthy residents of Sapporo found a prevalence of 70%-80% for individuals born before 1950[20]. For those residents born after 1950, the frequency of *H. pylori* infection increased at approximately 1% per birth year[20]. The prevalence of *H. pylori* infection, however, has been decreasing over the past several decades. The overall *H. pylori* seropositivity was 72.7% in 1974, 54.6% in 1984, and 39.3% in 1994, based on an assay of serum samples from 1015 healthy people living in several prefectures in central Japan[21]. As in other developed countries, a clear birth cohort effect has been observed for *H. pylori* infection in Japan, with younger generations experiencing a more rapid decline than older generations[22,23]. In a 2007 study involving 777 university students with a mean age of 19.6 years, *H. pylori* prevalence was only 14.7%[24].

China: The Chinese population has a high prevalence of *H. pylori* infection. A 2003 meta-analysis, based on studies published between 1990 and 2002, concluded that the prevalence of *H. pylori* infection for the entire Chinese population was approximately 58%[25]. Since 2003, numerous studies have also been conducted to examine the prevalence of *H. pylori* in healthy people in different regions of China, with reported prevalence ranging from 40% to 81%[26-29]. Generally, studies in rural areas found a higher prevalence of *H. pylori* than studies in urban areas. Furthermore, areas with high gastric cancer incidence generally have a higher prevalence of *H. pylori* infection than low-incidence areas.

Because *H. pylori* is acquired during childhood, some surveys of *H. pylori* prevalence in China have focused on children. One recent study reported a prevalence of 37.7% in children aged 10-19 years in Beijing and 25.5% in the same age group in Shandong[30]. Some studies suggest a downward trend in *H. pylori* seroprevalence in some regions; for example, a significant decrease was observed across age groups in Guangzhou[31]. Evidence on this subject, however, is fragmentary and inconclusive. In particular, it remains unclear whether the rate of decline is accelerating, especially in the younger segments of the population.

H. pylori colonization: Findings from observational epidemiologic studies addressing the association between H. pylori and gastric cancer risk

Japan: Both case-control and cohort studies have been conducted to estimate the degree of gastric cancer risk associated with *H. pylori* infection in the Japanese population. To date, all four prospective studies have shown a positive association, with relative risks (RRs) ranging from 1.0 to 5.1[32-35] (Table 2). In the prospective study that used the largest dataset (511 cases and 511 control subjects), Sasazuki *et al*[35] showed that the adjusted odds ratio (OR) of gastric cancer associated with *H. pylori* infection was 5.1, which is quite similar to the estimate of 5.9 for non-cardia gastric cancer in a combined analysis of 12 case-control studies nested within prospective cohorts[36]. Based on the substantial evidence from both case-control and cohort studies, it is clear that *H. pylori* infection is causally linked to gastric cancer in the Japanese population.

Table 2 Summary of findings on the associations between *H. pylori* carriage and risk of gastric cancer in prospective studies from Japan and China

Author[Ref.], yr	Country	Study design	Case patients /control subjects	Seroprevalence of *H. pylori* in cases *vs* controls (%)	ELISA kit used for measuring seroprevalence of *H. pylori*	OR (95% CI)
Watanabe *et al*[32], 1997	Japan	Nested case-control study	45/225	91.1 *vs* 75.6	Pirikaplate G *Helicobacter* enzyme immunoassay (Fujirebio Inc., Tokyo)	3.4 (1.2-9.9)
Sasazuki *et al*[35], 2006	Japan	Nested case-control study	511/511	93.5 *vs* 74.5	E Plate, produced by Eiken Kagaku Co.Ltd., Tokyo	5.1 (3.2-8.0)
Yamagata *et al*[33], 2000	Japan	Cohort study	1070 men and 1532 women at baseline	71.5 among men *vs* 62.4 among women	HM-CAP, Enteric Products Inc, Westbury, NY	Men: RR = 2.9 (1.1-7.4) Women: RR = 1.0 (0.3-3.0)
Yatsuya *et al*[34], 2004	Japan	Nested case-control study	202/394	88.6 *vs* 79.2	HM-CAP, Enteric Products Inc, Westbury, NY	Men: 1.7 (0.5-5.1) Women: 5.1 (1.6-16.5)
Yuan et al[38], 1999	China	Nested case-control study	188/548	86 *vs* 85	Locally Developed and Validated Assay	1.8 (1.1-3.1), but 3.7 (1.5-9.3) for subjects followed for 5 or more years
Limburg *et al*[39], 2001	China	Nested case-control study	181/192	62.0 *vs* 52.0	Antibodies to the whole cell antigen	1.6 (1.1-2.5)
Kamangar *et al*[12], 2007	China	Case-cohort study	Cardia 582/992 Noncardia 343/992	Cardia 81.0 *vs* 73.0 Noncardia 80.0 *vs* 73.0	IgG antibodies to whole-cell antigen	Cardia 1.6 (1.3-2.1) Noncardia 1.6 (1.2-2.1)

OR: Odds ratio; RR: Relative risk; CI: Confidence interval.

China: The majority of epidemiologic studies that examined the association between *H. pylori* infection and gastric cancer in China are retrospective case-control studies. Of 11 case-control studies included in a 2001 meta-analysis, all studies showed a positive association. The ORs ranged from 2.1 to 5.6, with a combined OR of 3.0[37].

This positive association was also observed in two prospective cohort studies. Yuan *et al*[38] reported that the OR was 3.7 for individuals seropositive for *H. pylori* who were followed for 5 or more years, on the basis of a nested case-control study within a cohort of Shanghai residents. A prospective, nested case-control study in Linxian, one of the highest-incidence regions in China, found that *H. pylori* seropositivity results in an approximately 2-fold increased risk of gastric cancer[39]. This result was confirmed by a 2007 case-cohort study, in which *H. pylori* was associated with a 1.6-fold increased risk of both cardia and non-cardia gastric adenocarcinomas[12].

H. pylori colonization: Findings from clinical studies, including both non-intervention and intervention studies

Japan: Several recent clinical studies have greatly improved our understanding of the role of *H. pylori* in the development of gastric cancer. Umemura *et al*[7] (2001) found that gastric cancer developed in 36 of 1246 *H. pylori*-infected patients but none of the 280 uninfected patients in a prospective study involving 1526 Japanese patients with peptic ulcers, gastric hyperplasia or non-ulcer dyspepsia. The results are convincing because *H. pylori* colonization was confirmed by a combination of tests, including endoscopy, biopsy, histology, a rapid urease test, and serologic testing. This seminal study thus offers compelling evidence that *H. pylori infection* is associated with the development of both intestinal and diffuse gastric cancers. Another important study, a multicenter, open-label randomized controlled trial followed 544 patients who underwent endoscopic resection of early gastric cancer, half of whom underwent eradication of colonizing *H. pylori*[8]. Eradication decreased the risk of developing metachronous gastric cancer by approximately 65%, even though these patients had already been diagnosed with early gastric cancer.

China: To determine whether *H. pylori* eradication reduces the incidence of gastric cancer at the population level in high-risk areas in China, Wong *et al*[40] (2004) conducted a randomized, placebo-controlled trial, using subjects without precancerous lesions. Unfortunately, however, this study was restricted by a short follow-up period and did not address whether those subjects with precancerous lesions experience a similar reduction in gastric cancer risk.

Cigarette smoking

Japan: Numerous epidemiologic studies over the past several decades have examined the association between cigarette smoking and gastric cancer risk in Japan, with the majority showing a significantly increased risk in current smokers when compared with those subjects who have never smoked. According to a systematic review and meta-analysis conducted by the Research Group for the Development and Evaluation of Cancer Prevention Strategies in Japan in 2006, the summary RR for current smokers were estimated to be 1.8 (95% CI: 1.5-2.1) in men and 1.2 (1.1-1.4) in women[41]. Based on these results, the research group concluded that there is convincing evidence that tobacco smoking moderately increases the risk of gastric cancer in the Japanese population. Approximately 28.4% of gastric cancers are related to cigarette smoking, according to data from the Hisayama Study, a population-based prospective study of the combined influence of cigarette smoking and *H. pylori* infection[42]. That study found that cigarette smoking is sig-

nificantly associated with increased risk of gastric cancer independent of *H. pylori* infection.

Although cigarette smoking is associated with an increased risk of gastric cancer, it remains unclear whether the observed positive association is homogeneous in terms of histologic type or anatomic location; such information has not been included in most previous studies. A cohort study was designed to address this question, incorporating complete histologic data. The results suggest that smoking significantly increases the risk of differentiated, but not undifferentiated, distal gastric cancer[43].

China: The association between cigarette smoking and gastric cancer has been investigated in a number of epidemiologic studies, including both case-control and cohort studies, but the results are inconsistent[44]. No association was found in a cohort study involving 9351 middle-aged adults in urban Shanghai[45]. Another cohort study showed a non-significant increase in risk, with an RR of 1.4 for current smokers[46]. In contrast, a recent prospective study of men in Shanghai showed that among nondrinkers, smokers have an 80% greater risk of gastric cancer, suggesting that cigarette smoking and alcohol consumption exert independent effects on gastric cancer risk[47].

High intake of salt/salty food and food sources of nitrosamines

Japan: Collective evidence from epidemiologic and experimental studies over the past several decades strongly suggests that high intake of salt/salty food is associated with an increased risk of gastric cancer in Japanese populations[9]. Japanese cohort studies dominate the published literature on gastric cancer epidemiology; of the 11 cohort studies included in a recent meta-analysis of salt consumption and gastric cancer risk, six of these studies came from Japan[10]. In four of these Japanese studies, a statistically significant association was observed, with the RR ranging from 2.2 to 5.4 at the highest intake level.

The positive association observed between salt/salty food intake and gastric cancer risk in epidemiologic studies is also supported by experimental evidence. Using chemical carcinogens such as *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine (MNNG), Tatematsu *et al*[6] reported the first experimental model of gastric carcinogenesis in *H. pylori*-infected Mongolian gerbils. Experiments with this model demonstrated that sodium chloride (NaCl) enhances the carcinogenic effects of MNNG and 4-nitroquinoline-1-oxide. Another notable finding is that salt and *H. pylori* act synergistically to promote the development of gastric cancer in Mongolian gerbils[48].

No cohort or case-control studies in Japan have published results on nitrite or nitrosamine intake in relation to gastric cancer risk; however, the association between gastric cancer and dietary intake of exogenous and/or endogenous nitrosamine, including meat, processed meat, preserved fish, and preserved vegetables, was examined in 11 cohort studies published between 1985 and 2005[49]. The results are inconsistent, but most studies show no statistically significant association.

China: Of the 45 case-control studies and 11 cohort studies that were included in a 2009 meta-analysis of salt consumption and gastric cancer risk, 13 case-control studies, but no cohort studies, focus on Chinese populations[10]. The associations of gastric cancer with intake of salt, salty fish, salty vegetables, pickled vegetables, salted and fermented soya paste, and other salted foods have been examined, with ORs for individuals at the highest intake level ranging from 1.1 to 2.6. Overall, these findings indicate that high intake of salt and salty food increase the risk of gastric cancer.

Neither cohort nor case-control studies have been conducted to examine the risk of gastric cancer in relation to nitrite or nitrosamine intake in China. One cohort study, however, found no significant association between processed meat consumption and gastric cancer risk[49]. Additionally, a number of case-control studies have found that high intake of preserved fish and preserved vegetables is significantly associated with increased risk of gastric cancer[49].

DISCUSSION

We aimed to clarify the similarities and differences in gastric cancer epidemiology in Japan and China by closely examining patterns of incidence, mortality rates and risk profiles. It can be difficult to compare data from two different countries because of differences in genetic susceptibility; environmental exposure; lifestyle; and the way each country defines, reports and interprets data. Commonalities emerge, however, when the data are carefully compared. First, gastric cancer still poses a tremendous health burden in both countries. Second, the prevalence of *H. pylori* remains high in adults, and *H. pylori* infection significantly increases the risk for gastric cancer. The magnitude of positive association may have been underestimated in studies from both countries if only conventional IgG enzyme-linked immunosorbent assay (ELISA) serology was used to detect past *H. pylori* exposure. Because atrophy of the gastric mucosa progresses with time, seroreversion may result from loss of infection. In an analysis restricted to early diffuse cancer, a very strong association with *H. pylori* infection was observed among all age groups[50]. In a 2001 Swedish study that combined IgG ELISA with CagA immunoblot to detect *H. pylori* exposure, the adjusted OR for noncardia gastric cancer was 21.0 (8.3-53.4) among *H. pylori*-positive subjects[51]. Third, almost all *H. pylori* strains are CagA-positive, and CagA plays a central role in *H. pylori*-induced gastric carcinogenesis[52]. Fourth, in addition to *H. pylori* infection, cigarette smoking and high intake of salt/salty food are two important risk factors for gastric cancer. Fifth, clinical studies have provided important insights into the effects of *H. pylori* eradication on the

development of gastric cancer.

Despite these similarities, there are significant differences in many aspects of gastric cancer epidemiology between Japan and China, including patterns in mortality and the prevalence of *H. pylori* infection, *H. pylori* strains, the magnitude of gastric cancer risk related to *H. pylori* infection, and associations with diet. Studies in China have found a wider variation in patterns of incidence and mortality than have studies in Japan. Because the highest rates of gastric cancer are often seen in economically undeveloped rural areas in China, reduction of the mortality rate in these high-risk areas should be given top priority. Because of the pivotal role of *H. pylori* infection in gastric carcinogenesis, trends in infection prevalence likely affect the incidence of gastric cancer. The decline in *H. pylori* prevalence may have occurred faster in Japan than in China. Furthermore, in Japan, the observed decrease in gastric cancer was more marked than in China, especially among 20-39 years old subjects, suggesting a clear cohort effect. Further research is required to determine whether such an effect has been or will be occurring in China. Although it is unclear why only a small percentage of individuals infected with *H. pylori* develop gastric cancer, differences in *H. pylori* strains (i.e., virulence factors), inflammatory responses, and environmental exposure may be important factors in determining individual susceptibility to gastric cancer. In an analysis of 419 *H. pylori* strains from Japanese subjects and 65 *H. pylori* strains from Chinese subjects, East Asian CagA type accounted for 94% and 93%, respectively, of the detected strains[51]. This result suggests that almost all Japanese and Chinese *H. pylori* strains are CagA-positive; however, differences in other virulence factors, such as VacA and OipA, also warrant further study.

Diet is commonly believed to play an important role in the development of gastric cancer[53]. Because of the complexity of diet and the limitations of questionnaire-based surveys, clarifying its precise role remains a major challenge in epidemiologic studies. Compared to China, Japanese cohort studies dominate the literature on the associations of gastric cancer with diet; in particular, salt/salty food and dietary *N*-nitroso compounds are associated with gastric cancer incidence. There is substantial evidence suggesting that high intake of salt/salty food significantly increases the risk of gastric cancer in the Japanese population. Similarly, numerous case-control studies in China strongly suggest a positive association between high intake of preserved fish and vegetables and gastric cancer risk. The role of *N*-nitroso compounds is also crucial in gastric carcinogenesis, but epidemiologic studies from both Japan and China do not provide a clear picture of this role, at least in part because the intake of *N*-nitroso compounds is notoriously difficult to measure.

There is a need to accelerate the reduction of gastric cancer incidence and mortality in both countries and to determine the most effective strategy for the prevention of gastric cancer. Cost-effective prevention strategies have been extensively discussed in Japan[54]; one difficult issue is whether to adopt a test-and-treat policy for asymptomatic individuals. The available data do not provide a clear picture of the optimal timing for *H. pylori* eradication to achieve the maximum benefit while doing the least harm. In China, tobacco control could confer substantial public health benefits. With 20% of the world's population, China produces and consumes about 30% of the world's cigarettes and suffers about a million deaths a year from tobacco[55]. Efforts to promote tobacco control and decrease salt consumption should effectively reduce incidence and mortality from gastric cancers.

We propose the following three avenues for potential collaborative work based on the comparison of gastric cancer epidemiology between Japan and China. First, data comparisons on *H. pylori* genotyping are useful for identifying those people at increased risk of neoplastic transformation. Second, because the prevalence of premalignant disease states in the general population is currently undefined, it is important to estimate the prevalence of precancerous lesions, such as chronic atrophic gastritis and gastric intestinal metaplasia, and their associations with *H. pylori* infection, on the basis of endoscopic findings and serologic tests. Third, a multidisciplinary study is needed to address the role of *N*-nitroso compounds in the development of gastric cancer because epidemiologic studies are limited by difficulties in the precise measurement of *N*-nitroso compound intake. It is a challenge to find common ground for international collaboration. However, the similarities between these two countries, namely a high incidence of gastric cancer and a high prevalence of *H. pylori* infection, along with differences in many aspects of gastric cancer epidemiology, provide an excellent opportunity for Sino-Japanese collaboration. Such collaborations will facilitate a more complete understanding of gastric cancer etiology and the development of more effective interventions to reduce the mortality and incidence of gastric cancers. Given the pivotal role of *H. pylori* in gastric carcinogenesis, screening strategies in both countries based on *H. pylori* infection status would be very powerful for developing appropriate and cost-effective screening programs.

COMMENTS

Background

Japan and China have the highest incidences of gastric cancer in the world. Although a trend of declining incidence has been observed over the past several decades, gastric cancer still poses a tremendous burden to populations in each country. Although numerous gastric cancer studies have been conducted in each country, this article is the first to clarify the similarities and differences in gastric cancer between Japan and China by closely examining both epidemiologic features, such as patterns of incidence and mortality rates, and risk profiles on the basis of extensive published literature.

Research frontiers

To address why only a minority of individuals with *Helicobacter pylori (H. pylori)* colonization develop gastric cancer, the authors need to elucidate the interacting roles of various strains of *H. pylori*, host factors, and other lifestyle/environmental factors in gastric cancer. The authors also need more evidence on the optimal timing for *H. pylori* eradication in the interest of preventing gastric cancer.

Innovations and breakthroughs

The authors found differences in many aspects of gastric cancer between Japan and China, including patterns of mortality, trends in prevalence of *H. pylori* infection, *H. pylori* strains, and risk profiles. Due to the pivotal role of *H. pylori* infection in gastric carcinogenesis, trends in its population prevalence are likely to affect gastric cancer incidence. The decline in *H. pylori* prevalence may have occurred faster in Japan than in China. In Japan, a more marked decrease in gastric cancer was observed, especially among those people aged 20-39 years old; this evidence suggests a clear cohort effect. It will therefore be intriguing to see whether such a cohort effect has occurred in China or will do in the future.

Applications

This article has implications for future collaborative studies between Japan and China. First, comparing data on *H. pylori* genotyping is useful for identifying those patients at increased risk of neoplastic transformation. Second, it is important to estimate the prevalence of precancerous lesions, such as chronic atrophic gastritis and gastric intestinal metaplasia, and to evaluate the distribution of *H. pylori* in high-risk populations, on the basis of endoscopic findings and serologic tests. Third, a multidisciplinary study is needed to address the role of *N*-nitroso compounds in the development of gastric cancer. Specifically, screening strategies based on *H. pylori* negativity or positivity in both countries would be very powerful in terms of developing appropriate and cost-effective screening programs.

Terminology

H. pylori colonizes the human stomach, and individuals with *H. pylori* infection have an increased risk of developing gastric cancer.

Peer review

This article compares factors associated with the risk for developing gastric cancer in *H. pylori*-infected individuals from China or Japan. It summarizes a large body of literature on the rates of *H. pylori* infection along with the links between smoking, high salt and nitrate diets and gastric cancer rates. This article should be well received, especially in Asian countries, where the prevalence of *H. pylori* infection and gastric cancer remains unacceptably high.

REFERENCES

1 **Parkin DM**, Whelan SL, Ferlay WJ, Teppo L, Thomas DB. Cancer Incidence in five continents Vol VIII. France: IARC Scientific Publication No. 155

2 Statistics and Information Department, Minister's Secretariat. Vital Statistics of Japan 1968-2007 (in Japanese). Tokyo: Ministry of Health, Labour and Welfare

3 **Zou XN**, Duan JJ, Huangfu XM, Chen WQ, Zhao P. Analysis of stomach cancer mortality in the national retrospective sampling survey of death causes in China, 2004 - 2005. *Zhonghua Yufang Yixue Zazhi* 2010; **44**: 390-397

4 **Fock KM**, Talley NJ, Fass R, Goh KL, Katelaris P, Hunt R, Hongo M, Ang TL, Holtmann G, Nandurkar S, Lin SR, Wong BC, Chan FK, Rani AA, Bak YT, Sollano J, Ho KY, Manatsathit S. Asia-Pacific consensus on the management of gastroesophageal reflux disease: update. *J Gastroenterol Hepatol* 2008; **23**: 8-22

5 **Tsugane S**, Sasazuki S. Diet and the risk of gastric cancer: review of epidemiological evidence. *Gastric Cancer* 2007; **10**: 75-83

6 **Tatematsu M**, Takahashi M, Fukushima S, Hananouchi M, Shirai T. Effects in rats of sodium chloride on experimental gastric cancers induced by N-methyl-N-nitro-N-nitrosoguanidine or 4-nitroquinoline-1-oxide. *J Natl Cancer Inst* 1975; **55**: 101-106

7 **Uemura N**, Okamoto S, Yamamoto S, Matsumura N, Yamaguchi S, Yamakido M, Taniyama K, Sasaki N, Schlemper RJ. Helicobacter pylori infection and the development of gastric cancer. *N Engl J Med* 2001; **345**: 784-789

8 **Fukase K**, Kato M, Kikuchi S, Inoue K, Uemura N, Okamoto S, Terao S, Amagai K, Hayashi S, Asaka M. Effect of eradication of Helicobacter pylori on incidence of metachronous gastric carcinoma after endoscopic resection of early gastric cancer: an open-label, randomised controlled trial. *Lancet* 2008; **372**: 392-397

9 **Tsugane S**, Sasazuki S, Kobayashi M, Sasaki S. Salt and salted food intake and subsequent risk of gastric cancer among middle-aged Japanese men and women. *Br J Cancer* 2004; **90**: 128-134

10 **Wang XQ**, Terry PD, Yan H. Review of salt consumption and stomach cancer risk: epidemiological and biological evidence. *World J Gastroenterol* 2009; **15**: 2204-2213

11 **Epplein M**, Shu XO, Xiang YB, Chow WH, Yang G, Li HL, Ji BT, Cai H, Gao YT, Zheng W. Fruit and vegetable consumption and risk of distal gastric cancer in the Shanghai Women's and Men's Health studies. *Am J Epidemiol* 2010; **172**: 397-406

12 **Kamangar F**, Qiao YL, Blaser MJ, Sun XD, Katki H, Fan JH, Perez-Perez GI, Abnet CC, Zhao P, Mark SD, Taylor PR, Dawsey SM. Helicobacter pylori and oesophageal and gastric cancers in a prospective study in China. *Br J Cancer* 2007; **96**: 172-176

13 **Peek RM**, Blaser MJ. Helicobacter pylori and gastrointestinal tract adenocarcinomas. *Nat Rev Cancer* 2002; **2**: 28-37

14 **Yamaguchi N**, Kakizoe T. Synergistic interaction between Helicobacter pylori gastritis and diet in gastric cancer. *Lancet Oncol* 2001; **2**: 88-94

15 **Yang L**. Incidence and mortality of gastric cancer in China. *World J Gastroenterol* 2006; **12**: 17-20

16 **Song F**, He M, Li H, Qian B, Wei Q, Zhang W, Chen K, Hao X. A cancer incidence survey in Tianjin: the third largest city in China-between 1981 and 2000. *Cancer Causes Control* 2008; **19**: 443-450

17 **Zheng W**, Jin F, Devesa SS, Blot WJ, Fraumeni JF, Gao YT. Declining incidence is greater for esophageal than gastric cancer in Shanghai, People's Republic of China. *Br J Cancer* 1993; **68**: 978-982

18 **He YT**, Hou J, Chen ZF, Qiao CY, Song GH, Meng FS, Jin HX, Chen C. Trends in incidence of esophageal and gastric cardia cancer in high-risk areas in China. *Eur J Cancer Prev* 2008; **17**: 71-76

19 **Yeh JM**, Goldie SJ, Kuntz KM, Ezzati M. Effects of Helicobacter pylori infection and smoking on gastric cancer incidence in China: a population-level analysis of trends and projections. *Cancer Causes Control* 2009; **20**: 2021-2029

20 **Asaka M**, Kimura T, Kudo M, Takeda H, Mitani S, Miyazaki T, Miki K, Graham DY. Relationship of Helicobacter pylori to serum pepsinogens in an asymptomatic Japanese population. *Gastroenterology* 1992; **102**: 760-766

21 **Fujisawa T**, Kumagai T, Akamatsu T, Kiyosawa K, Matsunaga Y. Changes in seroepidemiological pattern of Helicobacter pylori and hepatitis A virus over the last 20 years in Japan. *Am J Gastroenterol* 1999; **94**: 2094-2099

22 **Nakajima S**, Nishiyama Y, Yamaoka M, Yasuoka T, Cho E. Changes in the prevalence of Helicobacter pylori infection and gastrointestinal diseases in the past 17 years. *J Gastroenterol Hepatol* 2010; **25** Suppl 1: S99-S110

23 **Kobayashi T**, Kikuchi S, Lin Y, Yagyu K, Obata Y, Ogihara A, Hasegawa A, Miki K, Kaneko E, Mizukoshi H, Sakiyama T, Tenjin H. Trends in the incidence of gastric cancer in Japan and their associations with Helicobacter pylori infection and gastric mucosal atrophy. *Gastric Cancer* 2004; **7**: 233-239

24 **Shiotani A**, Miyanishi T, Kamada T, Haruma K. Helicobacter pylori infection and allergic diseases: epidemiological study in Japanese university students. *J Gastroenterol Hepatol* 2008; **23**: e29-e33

25 **Wang KJ**, Wang RT. Meta-analysis on the epidemiology of Helicobacter pylori infection in China. *Zhonghua Liuxingbing Xue Zazhi* 2003; **24**: 443-446

26 **Shi R**, Xu S, Zhang H, Ding Y, Sun G, Huang X, Chen X, Li X, Yan Z, Zhang G. Prevalence and risk factors for Helicobacter pylori infection in Chinese populations. *Helicobacter* 2008; **13**: 157-165

27 **Myhal ML**, Laux DC, Cohen PS. Relative colonizing abilities of human fecal and K 12 strains of Escherichia coli in

the large intestines of streptomycin-treated mice. *Eur J Clin Microbiol* 1982; **1**: 186-192
28 **Chen SL**, Xiao SD, Liu WZ, Xu WW, Pan Y. Comparison of seroepidemiology of Helicobacter pylori in Shanghai urban area during 1990 and 2001. *Weichangbing Xve* 2002; **7**: 146-148
29 **Pan RF**, Gong ST, Qu WJ, Zhen BX, He WY, Liang WQ, Chen GH. An analysis of H.pylori infection among children aged 2-12 years in Guangzhou. *Zhongguo Shiyong Erke Zazhi* 2006; **21**: 689-690
30 **Zhang DH**, Zhou LY, Lin SR, Ding SG, Huang YH, Gu F, Zhang L, Li Y, Cui RL, Meng LM, Yan XE, Zhang J. Epidemiology of Helicobacter pylori infection in Shandong and Beijing areas. *Zhonghua Neike Zazhi* 2009; **48**: 1004-1007
31 **Chen J**, Bu XL, Wang QY, Hu PJ, Chen MH. Decreasing seroprevalence of Helicobacter pylori infection during 1993-2003 in Guangzhou, southern China. *Helicobacter* 2007; **12**: 164-169
32 **Watanabe Y**, Kurata JH, Mizuno S, Mukai M, Inokuchi H, Miki K, Ozasa K, Kawai K. Helicobacter pylori infection and gastric cancer. A nested case-control study in a rural area of Japan. *Dig Dis Sci* 1997; **42**: 1383-1387
33 **Yamagata H**, Kiyohara Y, Aoyagi K, Kato I, Iwamoto H, Nakayama K, Shimizu H, Tanizaki Y, Arima H, Shinohara N, Kondo H, Matsumoto T, Fujishima M. Impact of Helicobacter pylori infection on gastric cancer incidence in a general Japanese population: the Hisayama study. *Arch Intern Med* 2000; **160**: 1962-1968
34 **Yatsuya H**, Toyoshima H, Tamakoshi A, Kikuchi S, Tamakoshi K, Kondo T, Mizoue T, Tokui N, Hoshiyama Y, Sakata K, Hayakawa N, Yoshimura T. Individual and joint impact of family history and Helicobacter pylori infection on the risk of stomach cancer: a nested case-control study. *Br J Cancer* 2004; **91**: 929-934
35 **Sasazuki S**, Inoue M, Iwasaki M, Otani T, Yamamoto S, Ikeda S, Hanaoka T, Tsugane S. Effect of Helicobacter pylori infection combined with CagA and pepsinogen status on gastric cancer development among Japanese men and women: a nested case-control study. *Cancer Epidemiol Biomarkers Prev* 2006; **15**: 1341-1347
36 **Helicobacter and Cancer Collaborative Group.** Gastric cancer and Helicobacter pylori: a combined analysis of 12 case control studies nested within prospective cohorts. *Gut* 2001; **49**: 347-353
37 **Xue FB**, Xu YY, Wan Y, Pan BR, Ren J, Fan DM. Association of H. pylori infection with gastric carcinoma: a Meta analysis. *World J Gastroenterol* 2001; **7**: 801-804
38 **Yuan JM**, Yu MC, Xu WW, Cockburn M, Gao YT, Ross RK. Helicobacter pylori infection and risk of gastric cancer in Shanghai, China: updated results based upon a locally developed and validated assay and further follow-up of the cohort. *Cancer Epidemiol Biomarkers Prev* 1999; **8**: 621-624
39 **Limburg P**, Qiao Y, Mark S, Wang G, Perez-Perez G, Blaser M, Wu Y, Zou X, Dong Z, Taylor P, Dawsey S. Helicobacter pylori seropositivity and subsite-specific gastric cancer risks in Linxian, China. *J Natl Cancer Inst* 2001; **93**: 226-233
40 **Wong BC**, Lam SK, Wong WM, Chen JS, Zheng TT, Feng RE, Lai KC, Hu WH, Yuen ST, Leung SY, Fong DY, Ho J, Ching CK, Chen JS. Helicobacter pylori eradication to prevent gastric cancer in a high-risk region of China: a randomized controlled trial. *JAMA* 2004; **291**: 187-194
41 **Koizumi Y**, Tsubono Y, Nakaya N, Kuriyama S, Shibuya D, Matsuoka H, Tsuji I. Cigarette smoking and the risk of gastric cancer: a pooled analysis of two prospective studies in Japan. *Int J Cancer* 2004; **112**: 1049-1055
42 **Shikata K**, Doi Y, Yonemoto K, Arima H, Ninomiya T, Kubo M, Tanizaki Y, Matsumoto T, Iida M, Kiyohara Y. Population-based prospective study of the combined influence of cigarette smoking and Helicobacter pylori infection on gastric cancer incidence: the Hisayama Study. *Am J Epidemiol* 2008; **168**: 1409-1415
43 **Sasazuki S**, Sasaki S, Tsugane S. Cigarette smoking, alcohol consumption and subsequent gastric cancer risk by subsite and histologic type. *Int J Cancer* 2002; **101**: 560-566
44 **Ladeiras-Lopes R**, Pereira AK, Nogueira A, Pinheiro-Torres T, Pinto I, Santos-Pereira R, Lunet N. Smoking and gastric cancer: systematic review and meta-analysis of cohort studies. *Cancer Causes Control* 2008; **19**: 689-701
45 **Yuan JM**, Ross RK, Wang XL, Gao YT, Henderson BE, Yu MC. Morbidity and mortality in relation to cigarette smoking in Shanghai, China. A prospective male cohort study. *JAMA* 1996; **275**: 1646-1650
46 **Tran GD**, Sun XD, Abnet CC, Fan JH, Dawsey SM, Dong ZW, Mark SD, Qiao YL, Taylor PR. Prospective study of risk factors for esophageal and gastric cancers in the Linxian general population trial cohort in China. *Int J Cancer* 2005; **113**: 456-463
47 **Moy KA**, Fan Y, Wang R, Gao YT, Yu MC, Yuan JM. Alcohol and tobacco use in relation to gastric cancer: a prospective study of men in Shanghai, China. *Cancer Epidemiol Biomarkers Prev* 2010; **19**: 2287-2297
48 **Shimizu N**, Inada K, Nakanishi H, Tsukamoto T, Ikehara Y, Kaminishi M, Kuramoto S, Sugiyama A, Katsuyama T, Tatematsu M. Helicobacter pylori infection enhances glandular stomach carcinogenesis in Mongolian gerbils treated with chemical carcinogens. *Carcinogenesis* 1999; **20**: 669-676
49 **Jakszyn P**, Gonzalez CA. Nitrosamine and related food intake and gastric and oesophageal cancer risk: a systematic review of the epidemiological evidence. *World J Gastroenterol* 2006; **12**: 4296-4303
50 **Kikuchi S**, Nakajima T, Kobayashi O, Yamazaki T, Kikuichi M, Mori K, Oura S, Watanabe H, Nagawa H, Otani R, Okamoto N, Kurosawa M, Anzai H, Kubo T, Konishi T, Futagawa S, Mizobuchi N, Kobori O, Kaise R, Sato T, Inaba Y, Wada O. Effect of age on the relationship between gastric cancer and Helicobacter pylori. Tokyo Research Group of Prevention for Gastric Cancer. *Jpn J Cancer Res* 2000; **91**: 774-779
51 **Ekström AM**, Held M, Hansson LE, Engstrand L, Nyrén O. Helicobacter pylori in gastric cancer established by CagA immunoblot as a marker of past infection. *Gastroenterology* 2001; **121**: 784-791
52 **Yamaoka Y**. Mechanisms of disease: Helicobacter pylori virulence factors. *Nat Rev Gastroenterol Hepatol* 2010; **7**: 629-641
53 **World Cancer Research Fund and American Institute for Cancer Research.** Food, nutrition and the prevention of cancer: a global perspective. 1st ed. 1997
54 **Graham DY**, Asaka M. Eradication of gastric cancer and more efficient gastric cancer surveillance in Japan: two peas in a pod. *J Gastroenterol* 2010; **45**: 1-8
55 **Peto R**, Chen ZM, Boreham J. Tobacco: the growing epidemic in China. *CVD Prevention and Control* 2009; **4**: 61-70

S- Editor Zhang SJ **L- Editor** O'Neill M **E- Editor** Zhang DN

Cancer Science
The official journal of the Japanese Cancer Association

Reduced serum vascular endothelial growth factor receptor-2 (sVEGFR-2) and sVEGFR-1 levels in gastric cancer patients

Shogo Kikuchi,[1,8] Yuki Obata,[2] Kiyoko Yagyu,[1] Yingsong Lin,[1] Toshifusa Nakajima,[3] Osamu Kobayashi,[4] Masahiro Kikuichi,[5,9] Ryo Ushijima,[6] Michiko Kurosawa[7] and Junko Ueda[1]

[1]Department of Public Health, Aichi Medical University, School of Medicine, Aichi; [2]Department of Pharmacy, Kinjogakuin University, Aichi; [3]Cancer Institute Hospital, Tokyo; [4]Kanagawa Cancer Center, Kanagawa; [5]Mitsui Memorial Hospital, Surgery, Tokyo; [6]Suifu Hospital, Surgery, Ibaraki; [7]Department of Epidemiology and Environmental Health, Juntendo University, School of Medicine, Tokyo, Japan

(Received October 28, 2010/Revised December 21, 2010/Accepted December 27, 2010/Accepted manuscript online January 10, 2011/Article first published online February 15, 2011)

The relationship between gastric cancer and serum vascular endothelial growth factor receptor-1 (sVEGFR-1) and sVEGFR-2, which are soluble form receptor proteins of vascular endothelial growth factor (VEGF), has not been extensively studied. VEGF, sVEGFR-1 and sVEGFR-2 were measured in the sera obtained before surgical operation from 164 gastric cancer patients and from 164 healthy controls matched for age and gender. Compared with controls, the cases showed elevated VEGF ($P < 0.01$) and reduced sVEGFR-1 ($P = 0.07$) and sVEGFR-2 ($P = 0.02$). The difference in VEGF levels was small among men and when the outcome was early cancer. The difference in sVEGFR-1 levels was significant or borderline significant only in men and when the outcome was diffuse type cancer. The difference in sVEGFR-2 levels was significant only in men and when the outcome was advanced or diffuse type cancer. The sensitivities and specificities of VEGF, sVEGFR-1 and sVEGFR-2 were all approximately 60%. For diffuse type cancer, sVEGFR-2 showed a sensitivity of 62.4% and a specificity of 63.4%, which was similar to serum pepsinogen. In conclusion, elevated VEGF and reduced sVEGFR-1 and sVEGFR-2 in serum are characteristic of gastric cancer patients, and the value of serum sVEGFR-2 in the diagnosis of diffuse type gastric cancer should be further evaluated. (*Cancer Sci* 2011; 102: 866–869)

Although the incidence and mortality of gastric cancer have been declining among the younger generation in Japan,[1] it remains as the second highest cause of cancer death.[2] Recently, it has been proposed that serum *Helicobacter pylori* antibody and pepsinogen values should be used for risk assessment of gastric cancer in adults,[3,4] and gastric cancer prevention programs are expected to become more cost-effective, if the programs do not target at subjects without *H. pylori* infection or abnormal serum pepsinogen values, who have very low risks of gastric cancer.[4,5] However, the sensitivity of serum pepsinogen is poor for diffuse type gastric cancer.[6] Vascular endothelial growth factor (VEGF) is a factor promoting vascularization, and it plays a role in both physical and malignant conditions.[7] Staining with VEGF antibodies has revealed the presence of VEGF in some malignant tissues.[8] Previous studies have shown that serum VEGF concentration is high in several cancers, such as breast and colon cancers.[9,10] In gastric cancer patients, elevated VEGF predicts a poor prognosis[8,11] and is often accompanied by other malignant factors such as TGFβ-1.[12]

The biological effects of VEGF are mediated by two receptor tyrosine kinases, VEGFR-1 and VEGFR-2, which are almost exclusively expressed within endothelial cells. In addition to VEGFR-1 and VEGFR-2, a soluble form of VEGF-R1 (sVEGFR-1), a naturally occurring and alternatively spliced variant, functions as a high-affinity receptor of VEGF. Compared to VEGFR-1, VEGFR-2 is more widely distributed and expressed in all vessel-derived endothelial cells. The VEGF/VEGFR-2 signaling pathway plays a crucial role in tumor angiogenesis. Although the exact role of VEGFR-1 remains controversial, the available evidence have shown that VEGFR-1 functions to limit VEGF/VEGFR-2 mediated angiogenesis with intact receptor acting as a decoy and soluble form creating inert receptors by dimerization with VEGFR-2 or sequestering free ligand.[7] Soluble form of VEGFR-2 (sVEGFR-2) as well as sVEGFR-1 can be detected in serum. Circulating VEGF is known to be higher in gastric cancer patients than in healthy subjects.[13] However, the data on circulating sVEGFR-1 and sVEGFR-2 levels are limited.

In this study, serum VEGF, sVEGFR-1 and sVEGFR-2 levels were compared between gastric cancer patients and matched healthy controls. Secondary analyses examined different subtypes of gastric cancer defined by progression stage and histopathological type. To evaluate the diagnostic accuracy of the VEGF, sVEGFR-1 and sVEGFR-2 levels, the optimal cutoff values, sensitivities and specificities for gastric cancer were calculated.

Materials and Methods

Subjects in this study were originally enrolled in our previous study; the details of the subject recruitment and data collection are provided elsewhere.[14,15] Briefly, sera were collected from 787 gastric cancer patients who were younger than 70 years of age and were admitted to the surgical division of nine hospitals in the Tokyo Metropolitan Area between June 1993 and July 1995. Phlebotomy of each patient was performed before cancer treatment (surgical operation or chemotherapy). The sera were also collected from 1007 apparently healthy subjects who were admitted for health screening programs between June 1993 and November 1994. Informed consent was obtained from all subjects. The diagnosis of cancer was confirmed, and other information, including histological types and progression stages, was collected from histopathological reports for resected or biopsy specimens.

In three of the nine hospitals, prognosis information for gastric cancer patients was available. Of the 571 patients from these three hospitals, 198 cases were randomly selected so that young patients were included, and the proportion of men and women were similar in each 10-year age group.

[8]To whom correspondence should be addressed.
E-mail: kikuchis@aichi-med-u.ac.jp
[9]Present address: Southern Tohoku Group Tokyo Hospital, Tokyo.

doi: 10.1111/j.1349-7006.2011.01860.x

Table 1. Characteristics of subjects

	Control	Case	*P*-value
Number of subjects	164	164	
Age (years)	53.9 ± 10.0*	54.0 ± 9.9*	Matched factor
Male/Female	78/86	78/86	Matched factor
Smoking dose (number of cigarettes per day multiplied by smoking years)			
No smoking history	84 (51.2%)	81 (49.4%)	$P = 0.43$
1–399	27 (16.5%)	23 (14.0%)	
400–799	22 (13.4%)	25 (15.2%)	
800+	21 (12.8%)	30 (18.3%)	
Unknown	10 (6.1%)	5 (3.0%)	
Drinking dose (amount of alcohol consumed [g] per week multiplied by drinking years)			
No drinking history	47 (28.7%)	54 (32.9%)	$P < 0.01$
Occasional/1–134.9	38 (23.2%)	28 (17.1%)	
135–1349.9	35 (21.3%)	27 (16.5%)	
1350+	19 (11.6%)	41 (25.0%)	
Unknown	25 (15.2%)	14 (8.5%)	
Helicobacter pylori seropositive†	105 (64.0%)	159 (97.0%)	$P < 0.01$

*Mean ± standard deviation. †Measured using J-HM-Cap (Kyowa Medex Co. Ltd., Tokyo).

Table 2. VEGF, sVEGFR-1 and sVEGFR-2 levels in cases and controls

	VEGF (pg/mL) Mean ± SD	sVEGFR-1 (pg/mL) Mean ± SD	sVEGFR-2 (pg/mL) Mean ± SD
Total			
Number of pairs	164	147	164
Controls	479.1 ± 350.8	56.96 ± 34.34	8853 ± 1888
Cases	640.6 ± 516.8	48.47 ± 32.45	8397 ± 2014
P-value*	$P < 0.01$	$P = 0.07$	$P = 0.02$
Male			
Number of pairs	78	71	78
Controls	511.6 ± 372.4	56.10 ± 36.26	9304 ± 1822
Cases	649.3 ± 517.6	42.58 ± 30.46	8343 ± 2186
P-value*	$P = 0.06$	$P = 0.02$	$P = 0.04$
Female			
Number of pairs	86	76	86
Controls	479.6 ± 329.4	55.82 ± 32.69	8443 ± 1864
Cases	632.8 ± 519.0	53.97 ± 33.47	8173 ± 1828
P-value*	$P < 0.01$	$P = 0.74$	$P = 0.28$

*Results from paired *t*-tests. VEGF, vascular endothelial growth factor; sVEGFR-1/2, serum vascular endothelial growth factor receptor-1/2.

Table 3. VEGF, sVEGFR-1 and sVEGFR-2 levels in cases and controls with respect to progression stage (early or advanced) and histopathological type (intestinal or diffuse)

	VEGF (pg/mL) Mean ± SD	sVEGFR-1 (pg/mL) Mean ± SD	sVEGFR-2 (pg/mL) Mean ± SD
Early gastric cancer (depth of tumor invasion is within submucosa)			
Number of pairs	78	70	78
Controls	485.4 ± 344.0	52.68 ± 30.79	8853 ± 1770
Cases	607.4 ± 422.8	46.43 ± 28.81	8811 ± 2075
P-value*	$P = 0.06$	$P = 0.24$	$P = 0.88$
Advanced gastric cancer (depth of invasion includes propria muscle)			
Number of pairs	86	77	86
Controls	473.3 ± 358.7	58.93 ± 37.23	8852 ± 2001
Cases	670.8 ± 590.2	50.32 ± 35.53	8021 ± 1891
P-value*	$P < 0.01$	$P = 0.16$	$P < 0.01$
Intestinal type gastric cancer			
Number of pairs	63	57	63
Controls	474.5 ± 391.3	50.64 ± 32.38	8501 ± 1764
Cases	658.6 ± 541.3	47.28 ± 30.96	8556 ± 2208
P-value*	$P = 0.03$	$P = 0.58$	$P = 0.87$
Diffuse type gastric cancer			
Number of pairs	101	90	101
Controls	481.9 ± 325.0	59.32 ± 35.29	9072 ± 1938
Cases	629.4 ± 503.4	49.22 ± 33.51	8297 ± 1887
P-value*	$P = 0.02$	$P = 0.06$	$P < 0.01$

*Results of paired *t*-tests. VEGF, vascular endothelial growth factor; sVEGFR-1/2, serum vascular endothelial growth factor receptor-1/2.

A healthy control was matched to each case based on age (within 2 years) and gender. In 34 pairs, the serum sample from either the case or the control had already been used up, so data on 164 matched pairs were available for this study. Based on the pathological information, cases were classified into early (depth of invasion was within submucosa) and advanced (depth of invasion includes propria muscle) gastric cancer or into intestinal and diffuse type cancers.

VEGF, VEGFR-1 and VEGFR-2 were measured in the sera with the commercial ELISA kit Quantikine from R&D systems (Minneapolis, MN, USA) for human VEGF, sVEGF R1 and sVEGF R2 by a researcher who was blind to the case status associated with the samples. Serum VEGF, sVEGFR-1 and sVEGFR-2 levels were compared between cases and controls by paired *t*-tests. To evaluate the diagnostic accuracy of the factors, the optimal cutoff values and the sensitivity and specificity were calculated for all, early, advanced, intestinal and diffuse type cancers. In these calculations, the controls were restricted to those who were paired to cases belonging to the specific classification.

Results

Table 1 shows the characteristics of the subjects. Although no remarkable difference in smoking was observed between cases and controls, the cases drank more alcohol and had a higher prevalence of *H. pylori*. VEGF and sVEGFR-2 levels were measured for all subjects, but the sVEGFR-1 level was measured only in 147 pairs because of insufficient sera.

The VEGF level was higher in cases than in controls (Tables 2,3), but the difference was weak among men and when the outcome was early cancer. Compared with controls, the cases tended to have lower sVEGFR-1 levels, and the difference was significant among male subjects and borderline significant when the outcome was diffuse type cancer. The sVEGFR-2 level was lower in cases of advanced or diffuse-type cancer than in their matched controls.

Table 4 shows the optimal cutoff values for VEGF, sVEGFR-1 and sVEGFR-2. Of the three factors, VEGF showed the best sensitivity and specificity, 63.5% and 65.1%, respectively, for intestinal-type cancer when the cut-off value was 415 pg/mL. sVEGFR-2 gave the best diagnostic accuracies for all advanced and diffuse type cancers where cut-off values (sensitivities and specificities) were 8520 pg/mL (61.0% and 60.4%), 8314 pg/mL (66.3% and 61.6%) and 8520 pg/mL (62.4% and 63.4%), respectively. For early gastric cancer, sVEGFR-1 gave the best sensitivity and specificity, 60.0% and 58.6%, respectively, when the cut-off value was 46.0 pg/mL.

Discussion

VEGF was elevated in gastric cancer patients compared to controls. The presence of VEGF in a gastric cancer lesion[11] and a

Table 4. Optimal cutoff values (sensitivity, specificity) of the factors for all, early, advanced, intestinal type and diffuse type cancers

Factor	All	Early	Advanced	Intestinal	Diffuse
VEGF (pg/mL)*	420 (60.4%, 57.9%)	428 (61.5%, 56.4%)	420 (58.1%, 60.5%)	415 (63.5%, 65.1%)†	428 (56.4%, 54.5%)
sVEGFR-1 (pg/mL)‡	45.6 (57.8%, 57.1%)	46.0 (60.0%, 58.6%)†	45.5 (57.1%, 55.8%)	40.7 (50.9%, 57.9%)	45.8 (58.9%, 60.0%)
sVEGFR-2 (pg/mL)‡	8520 (61.0%, 60.4%)†	8959 (55.1%, 52.6%)	8314 (66.3%, 61.6%)†	8400 (58.7%, 57.1%)	8520 (62.4%, 63.4%)†

*Positive is defined as the marker level being greater than or equal to the value given. †The best sensitivity and specificity of the three markers. ‡Positive is defined as the marker level being less than the value given. VEGF, vascular endothelial growth factor; sVEGFR-1/2, serum vascular endothelial growth factor receptor-1/2.

high level of circulating VEGF indicate a poor prognosis.[16–19] The result of the current study on VEGF is consistent with the results of previous studies.[13,20,21] The VEGF may have originated from gastric cancer cells[8] and the production and secretion may be increased with the progression of the cancer, but whether the cancer is intestinal or diffuse may have little influence on the VEGF level. It has been reported that *H. pylori* infection elevates serum VEGF level,[22,23] which can be a reason for the elevated VEGF level in gastric cancer patients. However, no association was observed between *H. pylori* serology and VEGF, sVEGFR-1 or sVEGFR-2 level in controls of this study.

Compared to the controls, the sVEGFR-1 and sVEGFR-2 levels were reduced in gastric cancer patients. One possibility is that the antibody used for ELISA recognizes the same or a near region as the ligand binds. Elevated VEGF levels may bind to these receptors and thereby reduce the sVEGFR-1 and sVEGFR-2 levels. Vascularization may promote cancer progression, and soluble VEGFR-1 and VEGFR-2 may act as decoys and disturb the binding of VEGF to VEGFR-2 on the surface of target cells. Reduced VEGFR-1 and VEGFR-2 levels and an elevated VEGF level stimulate the progression of gastric cancer and thus may be characteristic in gastric cancer patients.

Compared with VEGF, limited studies have examined circulating sVEGFR-1 level for gastric cancer and their role remains elusive. Colorectal cancer patients showed lower serum sVEGFR-1 level than controls did,[24] which is consistent with this study. Studies on pancreatic and biliary tract cancers gave similar results with this study on serum VEGF levels, but they showed higher sVEGFR-1 levels in patients than in controls.[25,26] Several studies to date have investigated relationships between sVEGFR-1 levels and prognosis as for several sites of cancers, which is inconsistent.[27] On sVEGFR-2 level, studies have been more limited. Further studies are warranted to clarify the role of sVEGFR-1 and sVEGFR-2 and their interactions with VEGF in the development of gastric cancer. The difference in the levels of the three factors between gastric cancer patients and controls was affected by gender, progression stage and histopathological type. The difference in the sVEGFR-1 level was not as clear as that for sVEFGR-2, which may be due to the obscure role of VEGFR-1 in vascularization. The differences in the VEGF and sVEGFR-2 levels were more striking for advanced cancer than early cancer, which can be explained by greater VEGF secretion from advanced gastric cancer tissues and by the binding of circulating sVEGFR-2. The difference in VEGF levels between matched cases and controls was smaller among men than women, while the differences in sVEGFR-1 and sVEGFR-2 levels between matched cases and controls were greater in men than in women. The underlying reason for the gender difference is unknown, but hormonal differences could exert some effect.

The difference in VEGF between matched cases and controls was similar between the intestinal and diffuse type cancers, whereas the difference in sVEGFR-1 and sVEGFR-2 levels was greater in the diffuse type cancer than in intestinal cancer. An explanation for the reduced sVEGFR-2 level in diffuse type gastric cancer is that advanced cancer was more frequent in diffuse type cancer than in the intestinal type. Actually, 54% of early and 69% of advanced cancers were diffuse types ($P = 0.06$). TGF-β1 is upregulated in patients with diffuse type gastric cancer[28,29] and TGF-β1 downregulates the expression of VEGFR-2 in endothelial cells.[30] These facts may be associated with the reduced sVEGFR-2 level in diffuse type gastric cancer. Serum pepsinogen II showed a sensitivity of 83.3% and a specificity of 76.9% for gastric cancer among those younger than 40 years of age,[31] although the sensitivity and specificity were weaker in those over 40 years. The sensitivities and specificities for the optimal cut-off values of VEGF, sVEGFR-1 and sVEGFR-2 were all approximately 60%, which is a somewhat unsatisfactory level. However, there were two interesting findings. One was that sVEGFR-2 showed a relatively good diagnostic accuracy compared with VEGF, although with VEGF, there was a smaller *P*-value than sVEGFR-2 in the paired *t*-test between cases and controls. The other finding was that sVEGFR-2 gave a similar diagnostic accuracy for diffuse type gastric cancer than serum pepsinogen. Serum pepsinogen, which is a good marker for gastric cancer and its risk,[32] does not show a good diagnostic accuracy for the diffuse type cancer.[6] When the diagnostic accuracy of serum pepsinogen for diffuse type cancer was calculated, and a positive result was defined as a pepsinogen I concentration not more than 70 ng/mL and the pepsinogen I to II ratio not more than 3.0,[33] the sensitivity and specificity were 65.3% and 59.4%, respectively. Compared with these values, the values for sVEGFR-2 of 62.4% and 63.4% were similar. Serum sVEGFR-2 can be used in the diagnosis of gastric cancer as the diagnostic accuracy of serum pepsinogen is not excellent. However, cautions are needed when using it to detect gastric cancer, because serum sVEGFR-2 is not specific for gastric cancer. The value of serum sVEGFR-2 in the diagnosis of gastric cancer, especially of the diffuse type, should be evaluated in further studies.

Because this study was not prospective, the differences in the serum levels of the markers may have been due to gastric cancer, and thus, the evaluation of the markers as risk indicators was impossible. We took this into consideration when interpreting the results. Another weakness of our study was that the measurement of the marker levels in the sera was performed after several years of frozen preservation. The preservation condition was not different between the cases and controls, and the measurement was performed by a researcher who was blinded to the case status for each serum sample. Thus, neither bias nor a difference in the preservation condition was expected to distort the results.

In conclusion, serum VEGF was elevated and sVEGFR-1 and sVEGFR-2 levels were reduced in gastric cancer patients. The difference in the levels of the three factors between gastric cancer patients and controls was affected by gender, progression stage and histopathological type. sVEGFR-2 showed a sensitivity and specificity for predicting diffuse type cancer that was similar to that of serum pepsinogen.

doi: 10.1111/j.1349-7006.2011.01860.x

Acknowledgments

This study was partly supported by grants-in-aid for General Scientific Research (No. 05304029) and for Scientific Research (No.16590521) by the Japanese Ministry of Education, Science, Sports and Culture.

Disclosure Statement

The authors have nothing to declare as financial disclosures.

References

1 Kobayashi T, Kikuchi S, Lin Y *et al.* Trends in the incidence of gastric cancer in Japan and their associations with *Helicobacter pylori* infection and gastric mucosal atrophy. *Gastric Cancer* 2004; **7**: 233–9.
2 Statistics and Information Department, Minister's Secretariat, Ministry of Health, Labour and Welfare. Cancer mortality. Vital statistics of Japan, 2008 (3): 136–46.
3 Kitahara F, Shimazaki R, Sato T *et al.* Severe atrophic gastritis with *Helicobacter pylori* infection and gastric cancer. *Gastric Cancer* 1998; **1**: 118–24.
4 Mukoubayashi C, Yanaoka K, Ohata H *et al.* Serum pepsinogen and gastric cancer screening. *Intern Med* 2007; **46**: 261–6.
5 Yanaoka K, Oka M, Yoshimura N *et al.* Risk of gastric cancer in asymptomatic, middle-aged Japanese subjects based on serum pepsinogen and *Helicobacter pylori* antibody levels. *Int J Cancer* 2008; **123**: 917–26.
6 Kang JM, Kim N, Yoo JY *et al.* The role of serum pepsinogen and gastrin test for the detection of gastric cancer in Korea. *Helicobacter* 2008; **13**: 146–56.
7 Ferrara N, Gerber HP, LeCouter J. The biology of VEGF and its receptors. *Nat Med* 2003; **9**: 669–76.
8 Maeda K, Chung YS, Ogawa Y *et al.* Prognostic value of vascular endothelial growth factor expression in gastric carcinoma. *Cancer* 1996; **77**: 858–63.
9 Nishimura R, Nagao K, Miyayama H *et al.* Higher plasma vascular endothelial growth factor levels correlate with menopause, overexpression of p53, and recurrence of breast cancer. *Breast Cancer* 2003; **10**: 120–8.
10 De Vita F, Orditura M, Lieto E *et al.* Elevated perioperative serum vascular endothelial growth factor levels in patients with colon carcinoma. *Cancer* 2004; **100**: 270–8.
11 Maeda K, Kang SM, Onoda N *et al.* Vascular endothelial growth factor expression in preoperative biopsy specimens correlates with disease recurrence in patients with early gastric carcinoma. *Cancer* 1999; **86**: 566–71.
12 Saito H, Tsujitani S, Oka S. The expression of transforming growth factor-beta1 is significantly correlated with the expression of vascular endothelial growth factor and poor prognosis of patients with advanced gastric carcinoma. *Cancer* 1999; **86**: 1455–62.
13 Karayiannakis AJ, Syrigos KN, Polychronidis A *et al.* Circulation VEGF levels in the serum of gastric cancer patients. *Ann Surg* 2002; **236**: 37–42.
14 Kikuchi S, Nakajima S, Kobayashi K *et al.* Effect of age on the relationship between gastric cancer and *Helicobacter pylori*. *Jpn J Cancer Res* 2000; **91**: 774–9.
15 Kikuchi S, Nakajima S, Kobayashi K *et al.* U-shaped effect of drinking and linear effect of smoking on risk for stomach cancer in Japan. *Jpn J Cancer Res* 2002; **93**: 953–9.
16 Woo IS, Kim KA, Jeon HM *et al.* Pretreatment serum endostatin as a prognostic indicator in metastatic gastric carcinoma. *Int J Cancer* 2006; **119**: 2901–6.
17 Ding S, Lin S, Dong X. Potential prognostic value of circulating levels of vascular endothelial growth factor-A in patients with gastric cancer. *In Vivo* 2005; **19**: 793–5.
18 Vidal O, Metges JP, Elizalde I. High preoperative serum vascular endothelial growth factor levels predict poor clinical outcome after curative resection of gastric cancer. *Br J Surg* 2009; **96**: 1443–51.
19 Oh SY, Kwon HC, Kim SH *et al.* Clinicopathologic significance of HIF-1α, p53, and VEGF expression and preoperative serum VEGF level in gastric cancer. *BMC Cancer* 2008; **8**: 123. doi:10.1186/1471-2407-8-123.
20 Al-Moundhri MS, Al-Shukaili A, Al-Nabhani M *et al.* Measurement of circulating levels of VEGF-A, -C, and -D and their receptors, VEGFR-1 and -2 in gastric adenocarcinoma. *World J Gastroenterol* 2008; **14**: 3879–83.
21 Ilhan N, Ilhan N, Ilhan Y *et al.* C-reactive protein, procalcitonin, interleukin-6, vascular endothelial growth factor and oxidative metabolites in diagnosis of infection and staging in patients with gastric cancer. *World J Gastroenterol* 2004; **10**: 1115–20.
22 Maciorkowska E, Marcinkiewicz S, Kaczmarski M *et al.* Inflammatory changes of the gastric mucosa of chosen growth factors in children. *Adv Med Sci* 2010; **55**: 59–66.
23 Mangia A, Chiriatti A, Ranieri G *et al. H. pylori* status and angiogenesis factors in human gastric carcinoma. *World J Gastroenterol* 2006; **12**: 5465–72.
24 Wei SC, Liang JT, Tsao PN *et al.* Preoperative serum placenta growth factor level is a prognostic biomarker in colorectal cancer. *Dis Colon Rectum* 2009; **52**: 1630–6.
25 Chang YT, Chang MC, Wei SC *et al.* Serum vascular endothelial growth factor/soluble vascular endothelial growth factor 1 ratio is an independent prognostic marker in pancreatic cancer. *Pancreas* 2008; **37**: 145–50.
26 Enjoji M, Nakamuta M, Yamaguchi K *et al.* Clinical significance of serum levels of vascular endothelial growth factor and its receptor in biliary disease and carcinoma. *World J Gastroenterol* 2005; **11**: 1167–71.
27 Wu FTH, Stefanini MO, Gabhann FM *et al.* A systems biology perspective on SVEGFR1: its biological function, pathogenic role and therapeutic use. *J Cell Mol Med* 2010; **10**: 528–52.
28 Komuro A, Yashiro M, Iwata C *et al.* Diffuse-type gastric carcinoma: progression, angiogenesis, and transforming growth factor β signaling. *J Natl Cancer Inst* 2009; **101**: 592–604.
29 Kinugasa S, Abe S, Tachibana M *et al.* Over expression of transforming growth factor-β1 in scirrhous carcinoma of the stomach correlates with decreased survival. *Oncology* 1998; **55**: 582–7.
30 Mandriota SJ, Menoudt PA, Pepper MS. Transforming growth factor-β1 down-regulates vascular endothelial growth factor receptor 2/*flk-1* expression in vascular endothelial cells. *J Biol Chem.* 1996; **271**: 11500–5.
31 Kikuchi S, Wada O, Miki K *et al.* Serum pepsinogen as a new marker for gastric carcinoma among young adults. Research Group on prevention of gastric carcinoma among young adults. *Cancer* 1994; **73**: 2695–702.
32 Yanaoka K, Oka M, Mukoubayashi C *et al.* Cancer high-risk subjects identified by serum pepsinogen tests: outcomes after 10-year follow-up in asymptomatic middle-aged males. *Cancer Epidemiol Biomarkers Prev* 2008; **17**: 838–45.
33 Kitahara F, Kobayashi K, Sato T *et al.* Accuracy of screening for gastric cancer using serum pepsinogen concentrations. *Gut* 1999; **44**: 693–7.