いため，予後判明率を上げる努力を施設に強いることは過大な負担につながる．しかし，生存率算出において，院内情報のみで把握可能な予後情報のみを使用した場合と，役場照会を行いほぼ全例の予後を判明させた場合で算出した生存率を比較した先行研究では，予後判明率が高いほど生存率は高く算出される例が報告されている[3]．そのような偏りのある数値の算出を避けるため，予後追跡・生存率公表のモデルを示した全国がん(成人病)センター協議会加盟施設の生存率協同調査における公表指針では「予後(消息)判明率95%以上目標，90%未満は算定中止」としている[4]．今後，協力施設の負担を増やさずに予後判明率を上昇させるためには，院内がん登録，地域がん登録など公的なしくみにより予後情報を系統的に収集し，一定の個人情報保護の元，臓器がん登録へ円滑に提供する仕組みが必要であると考えられる．

また，登録症例のカバー率も共通の課題かもしれない．これは，臓器によって非常に大きな幅が見られた．もっとも精度の高い詳細情報を収集するためには対象を広げるよりも高度な専門施設に限って登録を行った方が良いという考え方もある．しかし，カバー率が低く偏りがあるサンプルから得られた結果は解釈が困難であるため，対象を絞るのならばその偏りの方向と程度に関する考察は必要である．

臓器がん登録は多くは外科医を中心に行われてきたことから手術症例が中心であると考えられがちであったが，今回調査した登録においては，多くが化学療法のみ，放射線療法のみの症例も登録対象としていることが判明した．しかし，実際収集された報告書から判明した手術症例の割合と，2007年全国の院内がん登録の登録例における手術症例の割合[5]と比較すると，それぞれ，大腸癌(87%(1998年) vs 73%)[6]，乳癌(99%(2007年) vs 93%)[7]，肝癌(31%(2004～2005年) vs 25%)[8]と，臓器がん登録で手術症例が多いことがわかる(胃癌，肺癌の報告書は切除例のみのため割愛)．院内がん登録は日本全体を代表しているわけではないことに留意すべきではあるが，手術症例が現時点で多く登録される印象を裏づける結果のひとつではある．

これまで臓器がん登録に対しては一般に公的機関による関与はほとんど行われてこなかった．2007年に作成された国のがん対策の方向性を定めたがん対策推進基本計画においても「臓器がん登録」としてその存在は認められているものの，その国のがん対策の位置づけや方向性については，「予後調査にあたって(中略)臓器がん登録との連携(中略)について更なる検討を行っていく．」と述べられているにすぎない[9]．これは，一つは臓器がん登録が，今回の調査で示されたように，数が多く多彩であるばかりでなく統一した窓口が存在せず，意思決定や連携がとりづらいことが一つの原因かもしれない．また，がん登録側も各専門分野に特化しており他臓器や公的機関と連携する必要性をあまり感じていないことや，自主性を重視して連携を避ける傾向にあったことも一因かもしれない．しかし，がん対策基本法が施行され国全体ががん対策に取り組む時勢にあって，その中心の医療を担う専門家団体がその情報収集に当たって分離している状態が良いのかどうかは少なくとも再検討する必要があるのではないかと考えられる．がん対策基本計画において，学会が果たすべき役割を明確にした上で(ガイドライン作成，専門医資格認定など)，臓器がん登録の役割を再検討し，役割に応じた公的連携を考慮すべきではないか．今後の多くの学会，がん登録主体が協力・連携して共通の課題を克服することで，学会・がん登録主体自身にとって良い方向へ作用するだけでなく，ひいては，国全体のがん対策の促進要因となることが望まれる．

(謝辞)

本研究の調査にご回答をいただきました，各臓器がん登録のご担当の先生方に感謝致します．

文　献

1) 児玉哲郎：臓器別がん登録における生存率調査の概要．JACR Monograph 7：32-34, 2001.
2) 独立行政法人国立がん研究センターがん対策情報センター：全国がん罹患モニタリング集計．http://ganjoho.ncc.go.jp/professional/statistics/monita.html (Accessed on 07.22.2010)
3) 木下洋子，味木和喜子，木下典子ほか：がん専門施設における生存率計測の標準化．癌の臨床 46：1197-1203, 2000.
4) 全がん協加盟施設の生存率協同調査・公表指針：http://www.gunma-cc.jp/sarukihan/seizonritu/sisin.html (Accessed on 4.16.2008)
5) 独立行政法人国立がん研究センターがん対策情報センター：がん診療連携拠点病院院内がん登録全国集計2007. http://ganjoho.jp/professional/statistics/hosp_c_registry.html (Accessed on 7.22.2010)
6) Registry Committee, Japanese Society for Cancer of the Colon and Rectum：Multi-Institutional Registry of Large Bowel Cancer in Japan Vol.24 Cases treated in 1998 (Prospective Registry Data).
7) 日本乳癌学会，登録委員会：全国乳がん患者登録調査報告－暫定版－第38号2007年次症例．
8) 日本肝癌研究会：第18回全国原発性肝癌追跡調査報告(2004～2005). 2009.
9) がん対策推進基本計画：http://www.mhlw.go.jp/shingi/2007/06/dl/s0615-1a.pdf (Accessed on 8.10.2010)

腫瘍内科，7(1)：56-61，2011

特集 がん対策基本法による研究・診療の変化

がん登録の進歩*

祖父江友孝**

Key Words：cancer control, cancer registry, incidence, survival

がん対策とがん登録

2006年の「がん対策基本法」成立により，わが国において事前に策定された計画に基づいて国および都道府県レベルでがん対策に取り組む方向性が明文化された．2002年にWHOも国家的がん対策プログラム（national cancer control programme）の推進を提唱している．その目的とするところは，第一に，がんの罹患率と死亡率を減少させることであり，第二に，がん患者とその家族のquality of life（QOL）を向上させることである．この2つの目的を達成するため，予防・早期発見・診断・治療・終末期ケアからなる一連のがん対策において，証拠に基づいた戦略を系統的にかつ公平に実行し，限られた資源を効率よく最大限に活用することが求められる．がん対策を正しく方向づけるには，がんの実態を正確に把握する必要がある．がん登録は，がんの実態を把握するための中心的な役割を果たし，がん対策を実施する上で必須の仕組みである．2007年に閣議決定された「がん対策推進基本計画」の中でも，がん登録は3つの重点的に取り組むべき課題のうちの一つにあげられた．

がん対策推進基本計画における全体目標の進捗

がん対策基本計画では，今後10年間の全体目標として，「がんによる死亡者の減少」および「すべてのがん患者およびその家族の苦痛の軽減ならびに療養生活の質の維持向上」の2つを設定した．「がんによる死亡者の減少」については，「がんの年齢調整死亡率（75歳未満）」を指標と定め，「今後10年間（2005～2015年）に20％減少させる」という数値目標を設定し，人口動態統計によりモニタリングを実施することが記述された．ただし，通常諸外国のがん計画に含まれている「がん罹患者の減少」は全体目標に加えられなかった．この理由としては，わが国では全国レベルでがん罹患をモニタリングする仕組みの精度が十分ではなかった点がある．一方，「すべてのがん患者およびその家族の苦痛の軽減ならびに療養生活の質の向上」については，これまでのところ指標の設定自体ができていない．また，全体として，個別目標と全体目標との体系づけができていないとの指摘がある．

2010年6月に公表されたがん対策推進基本計画中間報告書では，「がんによる死亡の減少」の進捗状況については，「基本計画策定の際に得られていた2005年のがんの年齢調整死亡率（75歳未満）の92.4を100％とすると，2008年のがんの年齢調整死亡率（75歳未満）の87.2は94.4％に相当する」と記述されている．数値目標を設定した上で，モニタリングを実施できた点は評価できるが，目標とした数値自体はまだ検討の余地がある．

がん登録の進捗状況

がん対策を進める上で，がんの実態を表す重要な指標として，がんの死亡率（数），罹患率（数），および生存率がある．このうち，罹患率（数），生存率は，がん登録により計測されるが，がん登録には，地域がん登録，院内がん登録，臓器がん登録の3種類がある．罹患率（数）を計測する唯一の仕組みが，地域がん登録である．一方，生存率は，地域がん登録，院内がん登録，臓器がん登録のそれぞれで計測が可能であるが，目的，対象とするがん患者の範囲，収集する情報がそれぞれで異なる．以下，地域がん登録，院内がん登録，臓器がん登録の進捗状況について概説する．

1．地域がん登録

地域がん登録は，対象地域の居住者に発生したすべてのがんを把握することにより，がんの罹患率と地域レベルの生存率を計測する仕組みである．わが国では，1950年代より世界に先駆けて地域がん登録を開始した歴史があり，主に県を実施主体として実施されているが，法的基盤が弱く（健康増進法による努力義務），多くの地域で登録精度が低いのが最大の欠点である．2010年現在，38道府県1市で実施されているが（図1），世界各国のがん罹患データを収集した「5大陸のがん罹患」最新巻（第9巻，2007年）において，わが国から掲載されたのは7登録（宮城・山形・福井・愛知（モデル地区のみ）・大阪・広島市・長崎）のみであり，多くの登録は掲載されるために十分な登録精度を達成できていない．また，地域ごとに独自の工夫がなされたために，かえって作業手順の標準化が遅れていた．

現在，地域がん登録の標準化と精度向上のための体制整備は，厚生労働省研究班を中心とし

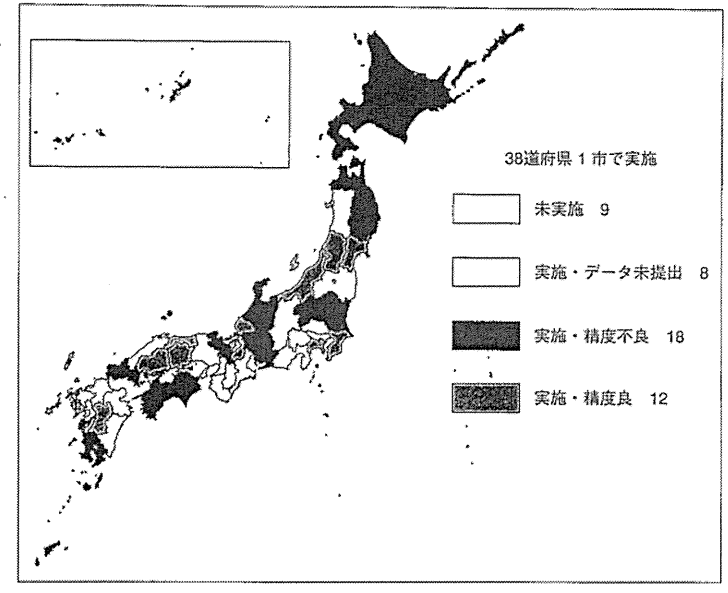

図1 地域がん登録の実施状況（2010）

* Recent progress of cancer registration in Japan.

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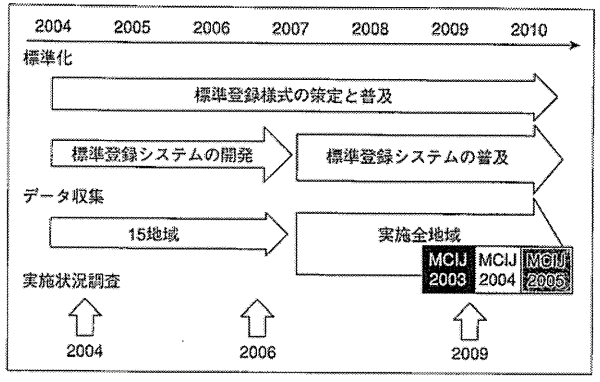

図2　地域がん登録に関する最近の活動
MCIJ；Monitoring of Cancer Incidence in Japan

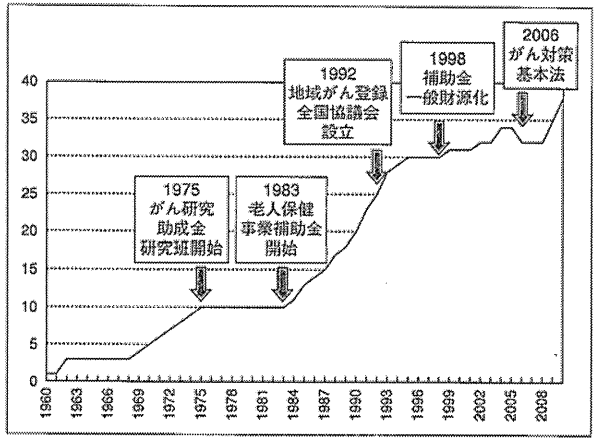

図3　わが国で実施されている地域がん登録数(県単位)の推移

て進められている(図2)．2004年に開始された第3次対がん総合戦略研究事業「がん罹患・死亡動向の実態把握に関する研究」班では，まず，標準登録様式(登録票，死亡転帰票，登録手順，集計表など)を定め，さらに，広島放射線影響研究所情報技術部が中心となり，山形県をモデルとして，標準登録様式を実装した標準登録システムの開発に着手した．2007年にはほぼ開発段階を終了して，その後普及に努め，現在21県で稼働するに至っている．また，がん対策基本法が成立した2006年以降，山梨，島根，長野，福島で地域がん登録が開始され，未実施県は9都県となっているが(図3)，これらの都県の多くで開始に向けての検討が進められており，近い将来，全県で地域がん登録が実施される状況も夢ではない．研究班によるデータ収集は，2004年当初，精度の比較的良好な15府県に限って行っていたが，2007年以降は原則実施全県からデータ収集をすることとし，2009年に実施した2005年診断例のデータ収集では，30府県から312,663

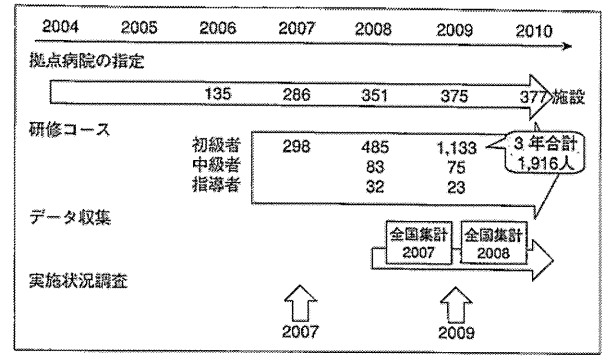

図4　院内がん登録に関する最近の活動

例を収集した．これらのうち，登録精度が一定以上の12府県(総人口の25%)のデータを用いて，全国罹患数を646,802例と推定した．また，これまでに3回(2004年，2006年，2009年)の実施状況調査を行っている．地域がん登録に関する情報の詳細は，以下のホームページを参照されたい．

・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．医療関係者向け「地域がん登録」(http://ganjoho.jp/professional/registration/index.html)
・地域がん登録全国協議会(http://www.jacr.info/)
・厚生労働省第3次対がん総合戦略事業「がん罹患・死亡動向の実態把握の研究」班(http://ncrp.ncc.go.jp/)

2．院内がん登録

院内がん登録は，当該施設でがんの診断・治療を受けた全患者について，がんの診断，治療，予後に関する情報を集約する仕組みである．当該施設における診療の実態を把握し，生存率を計測するなどの機能評価を行うとともに，地域がん登録への届出の役割も果たす．

2002年度から開始された「地域がん診療拠点病院」の指定要件に，院内がん登録システムの記述が含まれ，また，2006年度からは「地域がん診療連携拠点病院」(以下，拠点病院)と名称を変更して，その指定要件には，標準登録様式に基づく院内がん登録を実施することが明記された．さらに，2008年には，がん対策情報センターによる研修を受講した専任の院内がん登録の実務を担う者を1人以上配置すること，および，毎年院内がん登録の集計結果などを，がん対策情報センターに情報提供することとされた．

がん対策推進基本計画には，がん登録に関する個別目標として，「院内がん登録を実施している医療機関数を増加させるとともに，すべての拠点病院における院内がん登録の実施状況(診断から5年以内の登録症例の予後の判明状況など)を把握し，その状況を改善すること」および「すべての拠点病院において，5年以内に，がん登録の実務を担う者が必要な研修を受講すること」が記述された．

この間，拠点病院の指定数は年々増加し，現在は377(うち51が都道府県拠点)施設となっている(図4)．また，国立がん研究センターが実施するがん登録実務者研修のうち，初級者研修を修了した受講者数は2007～2009年の3年間に1,916名となり，拠点病院に少なくとも1人専任の実務担当者を配備するのに十分な人数となっている．また，拠点病院院内がん登録からのデータ収集をこれまで2回(2007年および2008年診断例)実施し，2008年診断例については，357施設より429,286例を収集した．これは，全国の新規診断例の58%をカバーしていると推定される．院内がん登録向け標準ソフトHos-CanRを無償で配布しており，200施設以上で利用されている．また，これまでに2回(2007年，2009年)の実施状況調査を行っている．院内がん登録に関する情報の詳細は，以下のホームページを参照されたい．

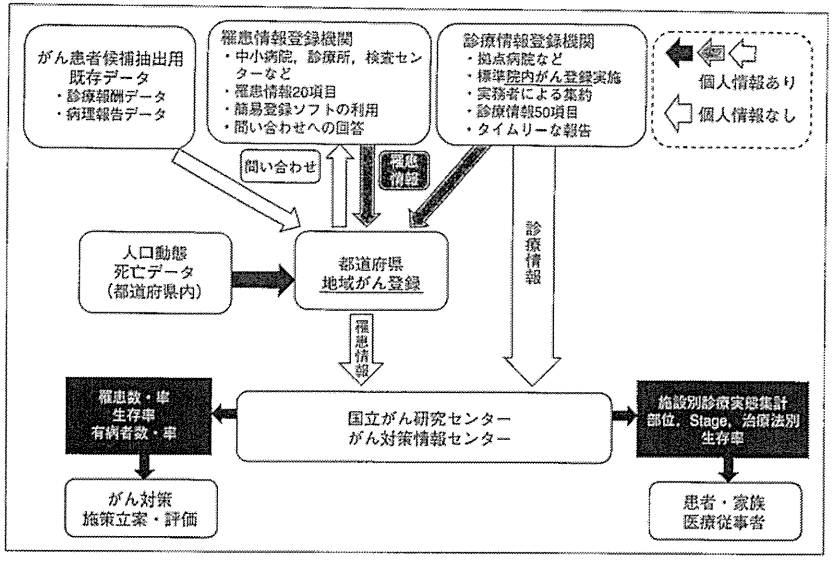

図5　がん登録のデータの流れ（将来案）

・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．

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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．

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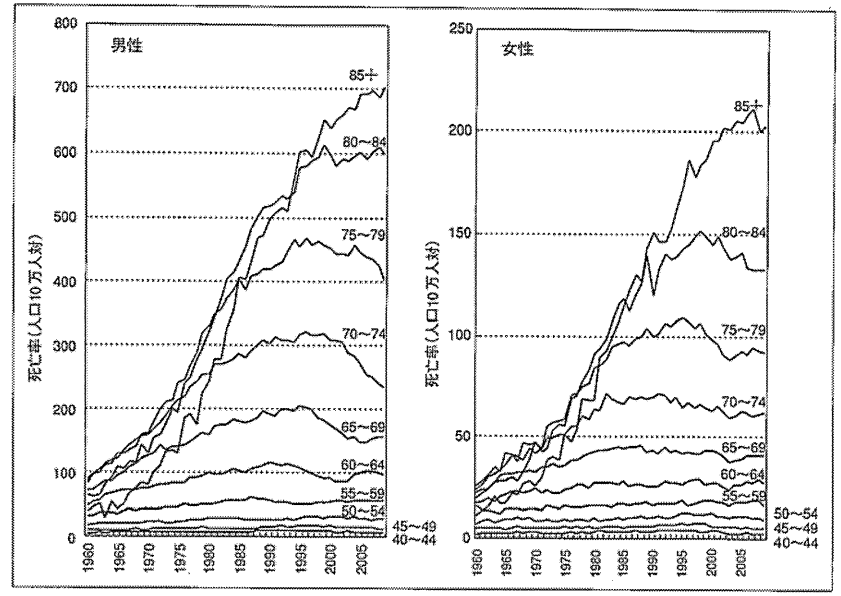

図1　年齢階級別肺がん死亡率の年次推移（1960～2009年）（文献[4]より引用改変）

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]．

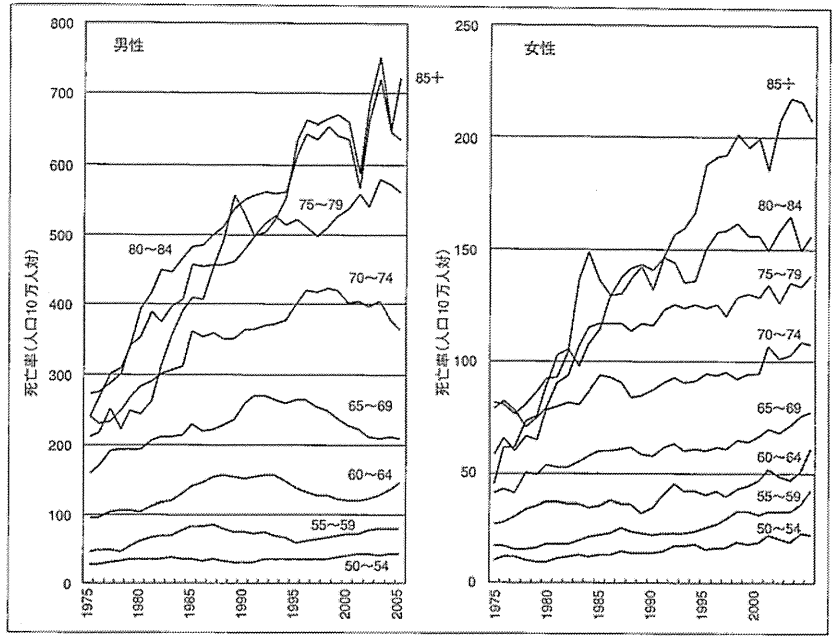

図2　年齢階級別肺がん罹患率の年次推移(1975～2005年)(文献[15]より引用改変)

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

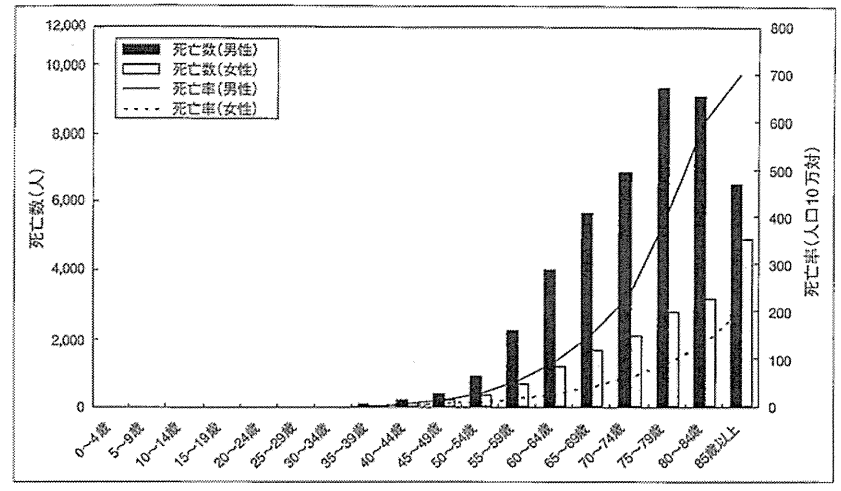

図3　年齢階級別肺がん死亡数・死亡率(2009年)(文献[16]より引用改変)

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

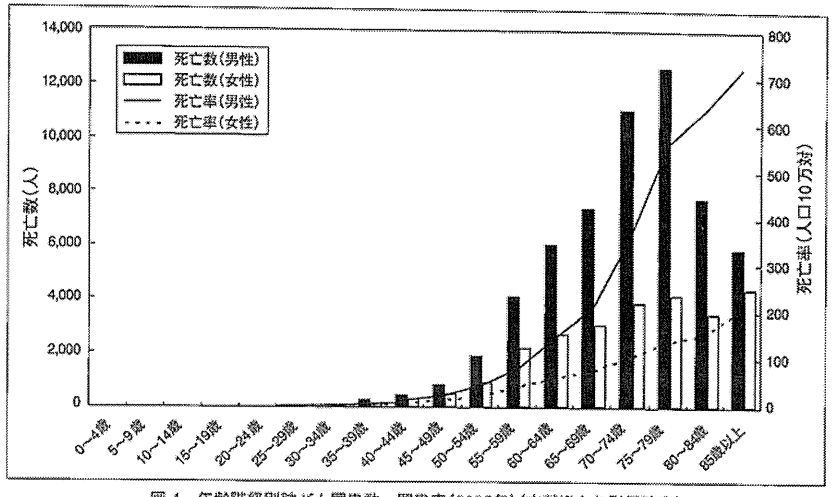

図4　年齢階級別肺がん罹患数・罹患率(2005年)(文献[15]より引用改変)

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[13]，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

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Trends of stomach cancer mortality in Eastern Asia in 1950–2004: comparative study of Japan, Hong Kong and Singapore using age, period and cohort analysis

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To characterize the temporal trends of stomach cancer mortality in Eastern Asia and to better interpret the causes of the trends, we performed age, period and cohort analysis (APC analysis) on the mortality rates in Japan, Hong Kong and Singapore during 1950–2004, as well as the rates in the US as a control population. For the APC analysis, Holford's approach was used to avoid the identification problem. Age-standardized mortality rates (ASMR) decreased consistently in all four areas during the observation period in both males and females. Japan had the highest ASMR in both sexes, followed by Singapore, Hong Kong and the US, but the differences in ASMR among the four areas diminished with time. The results of APC analysis suggested that the decreasing mortality rates in Eastern Asia were caused by the combination of decreasing cohort effect since the end of the 1800s and decreasing period effect from the 1950s. The US showed similar results, but its decreases in the period and cohort effect preceded those of Eastern Asia. Possible causes for the decrease in the cohort effect include improvement in the socioeconomic conditions during childhood and a decrease in the prevalence of *H. pylori* infection, while possible causes for the decrease in the period effect include a decrease in dietary salt intake and improvements in cancer detection and treatment. These findings may help us to predict future changes in the mortality rates of stomach cancer.

Introduction

Worldwide, stomach cancer is one the most common cancers. It was the most common cause of cancer mortality in the world until the mid-1990s; however, its mortality rate has been decreasing for several decades, and it has become a relatively rare cancer in North America and in the majority of Western European countries.[1] As of 2008, stomach cancer was still estimated to rank as the second most common cause of cancer deaths worldwide, accounting for ~10% of the global estimates.[2]

More than 70% of stomach cancer cases in the world occur in developing countries, and half the world total occurs in Eastern Asia, which has one of the highest mortality rates in the world.[2] Even in Eastern Asia, however, the mortality rate has been decreasing,[1] but we do not know whether the causes for this decrease are the same across the region or not, because of the paucity of comparative studies in the past.

One approach to characterizing the causes of mortality trends is age, period and cohort analysis (APC analysis), which estimates independent effects of the three time-dependent components on mortality.[3] Some studies in the past have applied APC analysis to stomach cancer mortality in Japan,[4,5] Taiwan[6] and Hong Kong.[7] However, the results of these studies cannot be compared because the analytical models used were not exactly the same. To our knowledge, no published study in the past focused on comparison of stomach cancer mortality trends in Eastern Asia using APC analysis.

To characterize the temporal trends of stomach cancer mortality in Eastern Asia and to better interpret the causes of the trends, we conducted a population-based time-series analysis of the mortality rates using APC analysis. We selected three areas in the region, namely Japan, Hong Kong and Singapore, which have submitted mortality records to the WHO Mortality database since the 1950s/60s, as well as the US as a comparison population. We describe the trends of stomach cancer mortality in these areas and apply APC analysis to the database to see if there is any difference in the effects of age, period and birth-cohort on the mortality trends. Based on the results, we discuss the causes of the trends in the four areas.

Key words: stomach cancer, mortality, age-period and cohort, Asia, the United States
Grant sponsors: Grant-in-Aid for Cancer Research, Grant-in-Aid for the Third Term Comprehensive 10-Year Strategy for Cancer Control (Japanese Ministry of Health, Labor and Welfare)
DOI: 10.1002/ijc.26080
History: Received 15 Feb 2011; Accepted 2 Mar 2011; Online 21 Mar 2011
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Material and Methods

Mortality, population data and age-standardized mortality rates

For the definition of stomach cancer, we used Code 151 in the International Classification of Diseases (ICD) Revisions Six, Seven, Eight and Nine, and Code C16 in the ICD Revision Ten. From the WHO Mortality database,[8] we obtained data on stomach cancer mortality and population at risk by age (0–79 year), sex and year of death (1950–2006) in Japan, Hong Kong, Singapore and the US. As to Hong Kong and Singapore, data were available only from 1960 to 1963, respectively. To describe the mortality trends, the mortality rate in each area was age-standardized by the world standard population.[9] These rates were smoothed using 5-year moving averages.

APC analysis

To perform APC analysis, the mortality and population data were tabulated in the respective areas, by 5-year age groups from the age of 30 through 79 years, and by 5-year calendar periods from 1950 to 2004. For Singapore, a truncated calendar period from 1965 was used. The model we used for APC analysis was described in detail elsewhere.[10] In short, in order to separately assess the effects of the three time-dependent components on the mortality trends, we formulated a Poisson regression model that included the patients' birth year and the age and calendar year of stomach cancer death as explanatory variables, and then applied the model to the mortality data from the four areas above. To avoid the "identification problem" inherent in the analyses, we employed the nonlinear (curvature) effect approach proposed by Holford.[3] In this approach, the full effect of each age, period and cohort (hereafter referred to as "the age effect," "the period effect" and "the cohort effect," respectively) was divided into two parts, namely "the linear part (the L part)" and "the nonlinear part (the NL part)." The L part roughly estimates the overall slope of each effect curve when it is approximated as a linear line, while the NL part is the deviation of the original effect curve from this approximated line. The L part of the age, period and cohort effects cannot be separated due to the identification problem, but the NL part of each effect can be estimated independently using Holford's approach. In addition, the L part of the age and period effects can be estimated, if we assume that the linear cohort effect is zero in the APC model. Likewise, the L part of the cohort effect can be estimated, assuming that the linear period effect is zero. As the reference for the age, period and cohort effects, we used the age group of 50–54 years, time period of 1975–1979, and birth cohort of 1918–1922, respectively. The maximum likelihood method was used to estimate parameters in our study. The goodness of fit was examined by the likelihood ratio statistic of the G square divided by the degrees of freedom of each parameter. For data processing, we used Microsoft Access, Microsoft Excel, and SAS 8.0. For the APC analysis, we used R 2.11.1 (R Development Core Team 2010).

Results

Trends of age-standardized mortality rates

Figure 1 shows the trends of age-standardized mortality rate (ASMR) of stomach cancer in Japan, Hong Kong, Singapore and the US, by sex for the period of 1952–2004, using 5-year moving averages. Japan had the highest mortality in both sexes, followed by Singapore, Hong Kong and the US throughout the observation period. The ASMR decreased consistently in all four areas during the observation period in both sexes. After the 1960s to 2004, the absolute decrease was largest in Japan, followed by Singapore, Hong Kong and the US in both sexes. The mortality differences among Japan, Hong Kong, Singapore and the US diminished with time. The mortality rate ratios between the US and the three areas in Eastern Asia were relatively stable from the 1960s to the 1990s (data not shown), despite the rapid reductions in ASMR in Eastern Asia. Throughout the observation period, the male/female ratio of ASMR in each of the four areas was relatively constant, at 2–3, in accordance with observations in other parts of the world.[11]

APC analysis

Table 1 shows the goodness of fit of four different Poisson models applied to the age-specific mortality rates in Japan, Hong Kong, Singapore and the US by sex. These models used different combinations of the three time-dependent parameters. Among the four models, the age-period-cohort model (the APC model), which uses all three parameters, had the smallest likelihood ratio statistic ($G2/\Delta df$) and was not significant at the 5% statistical significance level in any area or either sex. This means that the APC model was acceptable and that, among all of the models, it was estimated to be the most appropriate one for all areas for both sexes. Therefore, we decided to use the APC model in our study, and all of the discussion hereafter is about this model.

Figure 2 shows the trends of the age, period, and cohort effects during the observation period in the four areas, by sex. The Y-axis for each effect represents the natural logarithm of the relative mortality rate of stomach cancer at the corresponding age, calendar year of death, or birth year of the patients. The characteristics of the trends in each effect can be described as follows:

Age effect. The age effect increased approximately linearly with increasing age in all four areas in both sexes. At all ages after 50–54 years, the effect was greater in males than in females in Eastern Asia.

Period effect (calendar year). The period effects in Japan, Hong Kong and Singapore showed a constant decrease during the observation period in both sexes. In Japan, the decrease was slow from the 1950s to the 1960s and accelerated after the 1970s, while, in the US, the decrease was more

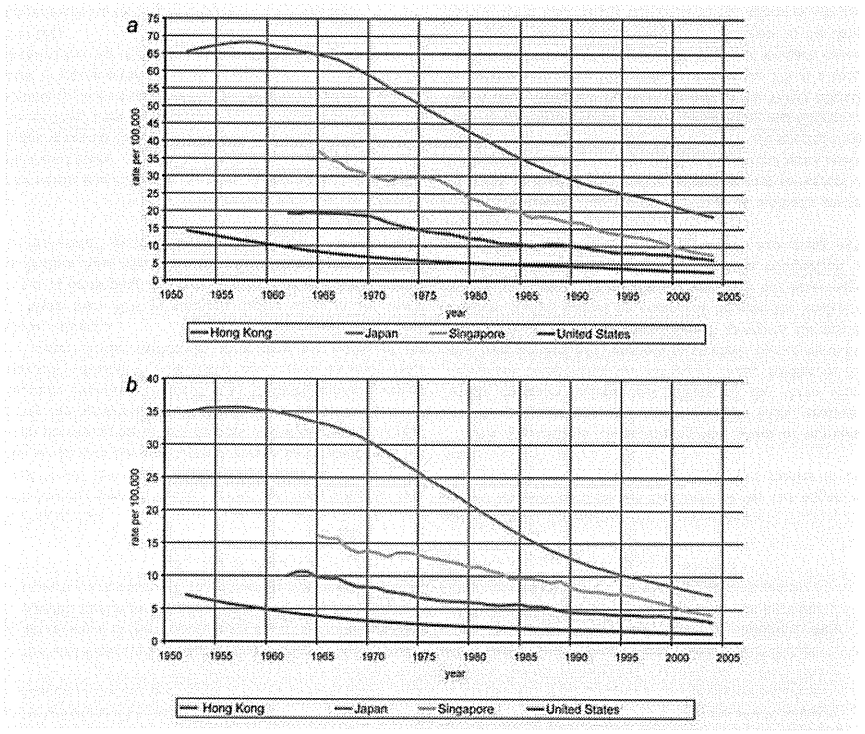

Figure 1. (*a*) Trends of age-standardized mortality rates of stomach cancer among males aged 0–79 years in Japan, Singapore, Hong Kong and the US. (*b*) Trends of age-standardized mortality rates of Stomach Cancer among females aged 0–79 years in Japan, Singapore, Hong Kong and the US.

rapid than in Japan from the 1950s, but slightly decelerated after the 1980s. The overall decrease was relatively constant in Hong Kong and Singapore, with a greater reduction in males than in females.

Cohort effect (birth year). In both sexes, Japan, Hong Kong and Singapore showed a constant decrease in the cohort effect from the end of 1800s to 1960s. Hong Kong and Singapore showed a fluctuating curve in the younger cohort due to the smaller number of deaths. When compared to the US, the decrease in Eastern Asia was slower from the end of the 1800s to the early 1900s, but accelerated thereafter to the 1960s. This decrease was most remarkable in Japan after the 1950s. In contrast, the US showed an earlier and more rapid decrease from the 1870s, but the decrease decelerated after the 1950s and leveled off to the 1960s.

Discussion

To the best of our knowledge, this is the first published report that focused on comparison of stomach cancer mortality trends in Eastern Asia using APC analysis. The age and birth year of the patients and the calendar years during which they lived, are the three major time-dependent factors that can independently influence the time-trends of cancer mortality. APC analysis is a kind of ecological study that can estimate the effects of the three time-dependent parameters. In the process of carcinogenesis under the multistage model,[12,13] each of the three variables is considered to have a distinct biological meaning. For example, exposure to carcinogens that are involved in the primary stages of carcinogenesis (initiators) may produce cohort effects, whereas exposure to carcinogens that are involved at later stages (promoters) may produce period effects. On the other hand, control

Table 1. Goodness-of-fit of four different Poisson models for stomach cancer mortality rates

		Men		Women	
Countries and Poisson models	Δdf	G2	G2/Δdf	G2	G2/Δdf
Japan					
Age-period-cohort model	72	1627.8	22.6	1634.2	22.7
Age-period model	90	13142.6	146.0	5207.6	57.9
Age-cohort model	81	3860.4	47.7	9995.1	123.4
Age only model	100	256354.5	2563.5	208189.8	2081.9
Singapore					
Age-period-cohort model	48	55.8	1.2	48.0	1.0
Age-period model	63	196.4	3.1	90.7	1.4
Age-cohort model	54	76.9	1.4	56.0	1.0
Age only model	70	1672.4	23.9	643.3	9.2
Hong Kong					
Age-period-cohort model	56	66.9	1.2	80.5	1.4
Age-period model	72	203.0	2.8	118.7	1.6
Age-cohort model	63	95.3	1.5	90.1	1.4
Age only model	80	1582.3	19.8	846.2	10.6
USA					
Age-period-cohort model	72	151.4	2.1	90.1	1.3
Age-period model	90	950.3	10.6	790.8	8.8
Age-cohort model	81	902.6	11.1	578.1	7.1
Age only model	100	116590.0	1165.9	73082.8	730.8

Goodness of fit is not sufficient for models indicated by asterisks (Likelihood ratio test: $*p < 0.01$, $**p < 0.001$).
Δdf: the difference in the degrees of freedom between each model and the original model of "m × n" parameters, where "m" and "n" mean the number of age strata and the period strata, respectively.

measures against cancer, such as introduction of a screening program or improvements in diagnosis and treatment, may also produce period effects in the mortality trends, if these control measures are widely accepted in the target population. By using APC analysis, we can estimate when and how each of the three time-dependent parameters influenced the mortality trends, which helps us to theorize regarding the etiology of the observed trends. However, this analytical method suffers from "the identification problem," and various approaches have been proposed to overcome this problem by adding probably but not necessarily-validated parameters. In our approach, identification of the three variables was made possible by application of the nonlinear effect of each variable and the linear effect of its shrinkage model. Our approach is based on minimal statistical assumptions, and its results should have minimal noise coming from those assumptions.

The ASMRs of stomach cancer decreased steadily in all four areas during the observation period. The absolute decrease was greater in Eastern Asia than in the US. The results of the APC analysis suggest that the decreased mortality rates in both sexes in the three Eastern Asian areas after the 1950s were caused by the combination of a decreasing cohort effect since the end of the 1800s and decreasing period effect from the 1950s. We noted similar trends in the US. Our findings are in line with the findings of a recent study by Malvezzi et al.,[14] which analyzed stomach cancer mortality data in 42 European countries from 1950 to 2007.

Unlike the three Asian areas, however, the cohort effect in the US stopped decreasing from the 1950s in both sexes, and leveled off thereafter. This finding may suggest that the mortality rates will stop decreasing in the US in the near future. This projection is supported by a recent study by Anderson et al.[15] who reported an increasing incidence of noncardia stomach cancer among white Americans born after 1952. On the other hand, in Japan, Hong Kong and Singapore, both the period and cohort effects kept decreasing through the end of their observation periods, which suggests that their mortality rates are likely to continue to decrease, at least for some time to come. If the latest trends in the period and cohort effects persist in the four areas, their mortality rates will become even more similar in the future.

The decrease in the cohort effect from the end of the 1800s shown in our study was also observed in previous studies that applied APC analysis to the stomach cancer mortality in Taiwan[6] and Hong Kong,[7] and to incidence in Sweden[16] and Spain,[17] whereas using different analytical approaches. We have no conclusive explanation for the cause of this decrease, but improved socioeconomic conditions (SEC) during childhood in

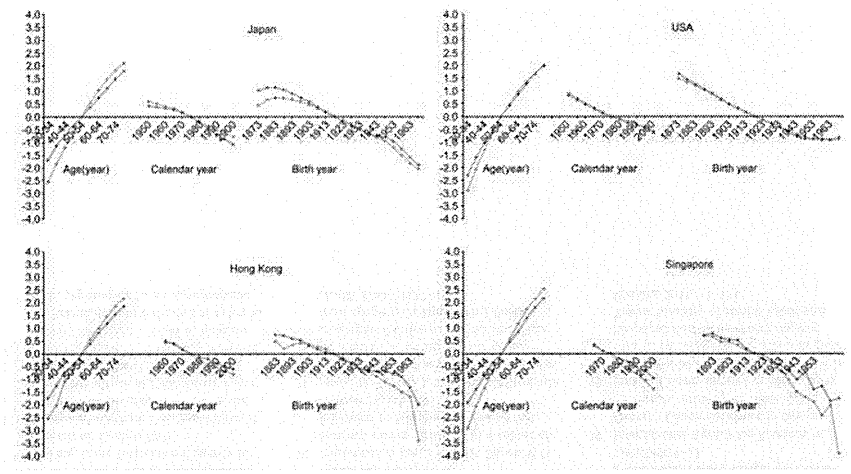

Figure 2. Age, period and cohort effect on stomach cancer mortality in males (blue circle) and females (red circle).

these populations may partly explain the finding. A prospective cohort study in Scotland demonstrated that men who had adverse SEC in childhood had higher stomach cancer mortality, independent of their SEC in adulthood.[18] At least two hypotheses for the underlying mechanisms are possible for this correlation, namely (*i*) an increased biological susceptibility to illness incurred directly by adverse conditions in childhood and (*ii*) unhealthy life behaviors acquired /triggered through childhood environments and maintained/developed through adulthood.[19] For stomach cancer, factors such as poor nutrition[20] and smoking habit[21] can be examples of causes under these mechanisms.

One of the most plausible explanations for the observed decrease in cohort effect, which is closely related to childhood SEC and firmly based on evidence from biological, clinical and epidemiological studies, is the decreasing prevalence of *Helicobacter pylori* (*H. pylori*) infection in younger generations. A study in the US demonstrated that *H. pylori* prevalence among adults was inversely related to SEC during childhood, even after adjustment for SEC in adulthood.[22] In the three areas in Eastern Asia, public health conditions were inferior to those of the US and Western Europe at least until the early 1900s, but drastic improvements took place after World War II with economic developments in these areas.[7] One study on the prevalence of *H. pylori* infection among healthy Japanese adults of different generations demonstrated that the prevalence decreased gradually from those born in the 1950s through those born in the 1980s.[23] In our study results, the cohort effect in Japan showed an accelerated decrease from the 1950s on, which should reflect the decreasing prevalence of *H. pylori* infection. Also, the rapid decrease in the cohort effect in the US from the 1870s should partly reflect the decrease in the prevalence that preceded the decrease in Eastern Asia.[24,25]

We also found a consistent decrease in the period effect since the 1960s/70s in the three Asian areas, as well as a similar but earlier decrease in the US. One potential cause for the consistent decrease in the period effect is decreased incidence due to a change in environmental factors. Immigrant studies in the US from the 1960s to 1980s[26,27] demonstrated decreased incidence rates of stomach cancer among first-generation immigrants from Eastern Asia, compared to the rates in their native countries. These findings support the role of environmental factors on stomach cancer incidence. One of the most likely environmental factors related to stomach cancer incidence is dietary salt and *N*-nitroso compound intake (hereafter collectively mentioned as "salt intake"). In Mongolian gerbils infected with *H. pylori*, high salt diets promoted gastric carcinogenesis dose-dependently.[28] Also, in humans, several epidemiological studies, including those on Japanese and Singaporean populations, have demonstrated a correlation between the amount of salt intake and stomach cancer incidence.[29,30]

A decrease in salt intake has been documented in Japan from the prewar era. The salt intake in Japan decreased gradually from 1930s to 2004, according to the results from cross-sectional regional nutrition surveys[31,32] and the annual National Health and Nutrition Survey[33] by the National Institute of Health and Nutrition, Tokyo. For example, the daily salt intake in northeastern Japan, which was known for a very salty diet and high stomach cancer mortality, decreased gradually from 34 g per person in 1935, 27 g in

1952, to 23 g in 1965.[31,32] Salt intake also decreased in Osaka province in western Japan, known for their lower salt intake than in other provinces; it decreased from 25 g in 1937 to 14 g in 1965.[31,32] The observed decrease in salt intake during this period occurred partly due to improved transportation system of food and partly to an improved food storage system, including the introduction of industrial refrigerators. After the 1960s when the prevalence of refrigerators reached over 50% at the household level,[34] the intake decreased further. The National Health and Nutrition Survey, which started to report salt intake statistics since 1973, shows that the national average daily salt intake decreased from 14.5 g in 1973 to 10.7 g in 2004. We are not aware of long-term studies on the salt intake trends in Hong Kong or Singapore, but these two areas have been relatively affluent urban business centers in Eastern Asia, which were westernized as part of the British Commonwealth since the 19th century. It is likely that their dietary salt intake also deceased, as their food-transporting systems developed in the prewar period, and as the cold chain system advanced in the postwar period. Allowing for a time-lag of 20–30 years, decreased salt intake in Japan, Hong Kong and Singapore since the prewar period, should have contributed to decreased stomach cancer incidence after the 1960s. It is possible, however, that a synergistic interaction between salt intake and *H. pylori* infection exists in carcinogenesis of the stomach,[35] which could complicate interpretation of the period and cohort effects in the results of APC analysis. We need further data and analyses for consistent interpretation of these effects.

Apart from the temporal decrease in salt intake, other possible reasons for the decrease in the period effect are improved prognosis of stomach cancer after the 1970s due to (*i*) improvements in cancer treatment,[5,36] (*ii*) earlier detection of stomach cancer with increased use of endoscopy in the health care setting,[37] and (*iii*) in Japan, earlier cancer detection due to the introduction of a population-based stomach cancer screening program.[38] The accelerated decrease in the period effect in Japan after the 1970s may reflect a combination of these factors. This hypothesis is supported by data from the Osaka Cancer Registry,[39] which demonstrate that the 5-year relative survival of localized stomach cancer cases improved from 73% in the 1970s to 93% in the 1990s and that the proportion of localized cases increased from 28 to 47% during the same period.[40]

Our study has some limitations. First, the data available from the WHO mortality database were provided by the authority of the respective countries/areas, which may have substantial variation in the system of vital statistics collection and in the confirmation of causes of death. Therefore, comparability of data in the database may be limited. However, we assume that the database is reliable enough for interpretation of the general trends in the respective areas, which is most important for the purpose of our study. Second, we used data of Japan, Hong Kong and Singapore as representatives of Eastern Asia because these areas were able to provide mortality data over a longer period of time with reasonably good quality. These areas, however, are the most affluent in Eastern Asia, and the trends in mortality and the causes for their changes may differ from those in the less developed areas in the region.

In conclusion, our results suggest that the decreasing trend in stomach cancer mortality rates in Japan, Hong Kong and Singapore since the 1950s was due to decreases in both period and cohort effects. The changes observed in these effects were consistent with changes in established environmental risk factors and improvements in cancer detection and treatment. These findings may help predict future changes in stomach cancer mortality rates.

Acknowledgements

The authors thank Ms. Yasue Koutani (Osaka Medical Center for Cancer and Cardiovascular Diseases) for her technical assistance.

References

1. Bertuccio P, Chatenoud L, Levi F, Praud D, Ferlay J, Negri E, Malvezzi M, La Vecchia C. Recent patterns in gastric cancer: a global overview. *Int J Cancer* 2009;125:666–73.
2. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer* 2010;127:2893–2917.
3. Holford TR. The estimates of age, period and cohort effects for vital rates. *Biobetrics* 1983;39:311–24.
4. Hamajima N, Lee JA. Relationships of age, period, and birth cohort for stomach cancer mortality in Japan. *Jpn J Cancer Res* 1987;78:547–58.
5. Lambert R, Guilloux A, Oshima A, Pompe-Kirn V, Bray F, Parkin M, Ajiki W, Tsukuma H. Incidence and mortality from stomach cancer in Japan, Slovenia and the USA. *Int J Cancer* 2002;97:811–8.
6. Lee WC, Lin RS. Interactions between birth cohort and urbanization on gastric cancer mortality in Taiwan. *Int J Epidemiol* 1994;23:252–60.
7. Wong IO, Cowling BJ, Law SC, Mang OW, Schooling CM, Leung GM. Understanding sociohistorical imprint on cancer risk by age-period-cohort decomposition in Hong Kong. *J Epidemiol Commun Health* 2010;64:596–603.
8. The World Health Organization. WHO mortality database. Available at http://www.who.int/healthinfo/morttables/en/index.html (accessed Sept. 2009).
9. Doll R,Payne P,Waterhouse JAH, eds. Cancer incidence in five continents, vol.1. Geneva: Union Internationale Contre le Cancer, 1966.
10. Takahashi H, Okada M, Kano K. Age-period-cohort analysis of lung cancer mortality in Japan, 1960–1995. *J Epidemiol* 2001;11:151–9.
11. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. *CA Cancer J Clin* 2005;55:74–108.
12. Doll R. The age distribution of cancer: implications for models of carcinogenesis. *J R Stat Soc Ser A* 1971;134:133–6.
13. Peto R. Epidemiology, multistage models and short term mutagenicity tests. In: Hiatt HH, Watson JD, Winsten JA, eds. Origins of human cancer, Book C: Human risk assessment. New York: Cold Spring Harbor Laboratory, 1977. 1403–28.

14. Malvezzi M, Bonifazi M, Bertuccio P, Levi F, La Vecchia C, Decarli A, Negri E. An age-period-cohort analysis of gastric cancer mortality from 1950 to 2007 in Europe. *Ann Epidemiol* 2010;20:898–905.
15. Anderson WF, Camargo MC, Fraumeni JF, Jr, Correa P, Rosenberg PS, Rabkin CS. Age-specific trends in incidence of noncardia gastric cancer in US adults. *JAMA* 2010;303:1723–8.
16. Hansson LE, Bergström R, Sparén P, Adami HO. The decline in the incidence of stomach cancer in Sweden 1960-1984: a birth cohort phenomenon. *Int J Cancer* 1991;47:499–503.
17. Aragonés N, Pollán M, López-Abente G, Ruiz M, Vergara A, Moreno C, Moreo P, Ardanaz E. Time trend and age-period-cohort effects on gastric cancer incidence in Zaragoza and Navarre, Spain. *J Epidemiol Commun Health* 1997; 51:412–7.
18. Smith GD, Hart C, Blane D, Hole D. Adverse socioeconomic conditions in childhood and cause specific adult mortality: prospective observational study. *BMJ* 1998;316:1631–5.
19. Lundberg O. The impact of childhood living conditions on illness and mortality in adulthood. *Soc Sci Med* 1993;36: 1047–52.
20. Kono S, Hirohata T. Nutrition and stomach cancer. *Cancer Causes Control* 1996;7:41–55.
21. IARC. IARC Monographs on the evaluation of carcinogenic risks to humans, vol. 83: Tobacco smoke and involuntary smoking. Lyon: International agency for Research on Cancer, 2004.
22. Malaty HM, Graham DY. Importance of childhood socioeconomic status on the current prevalence of *Helicobacter pylori* infection. *Gut* 1994;35:742–5.
23. 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; 102:760–6.
24. Brown LM. *Helicobacter pylori*: epidemiology and routes of transmission. *Epidemiol Rev* 2000;22:283–97.
25. Rupnow MF, Shachter RD, Owens DK, Parsonnet J. A dynamic transmission model for predicting trends in *Helicobacter pylori* and associated diseases in the United States. *Emerg Infect Dis* 2000;6: 228–37.
26. Kamineni A, Williams MA, Schwartz SM, Cook LS, Weiss NS. The incidence of gastric carcinoma in Asian migrants to the United States and their descendants. *Cancer Causes Control* 1999;10: 77–83.
27. Kolonel LN, Hinds MW, Hankin JH. Cancer patterns among migrants and native-born Japanese in Hawaii in relation to smoking, drinking, and dietary habits. In: Gelboin HV, eds. Genetic and entironmental factors in experimental and human cancer. Tokyo: Japan Science Society Press, 1980. 327–40.
28. Kato S, Tsukamoto T, Mizoshita T, Tanaka H, Kumagai T, Ota H, Katsuyama T, Asaka M, Tatematsu M. High salt diets dose-dependently promote gastric chemical carcinogenesis in *Helicobacter pylori*-infected Mongolian gerbils associated with a shift in mucin production from glandular to surface mucous cells. *Int J Cancer* 2006; 119:1558–66.
29. Tsugane S. Salt, salted food intake, and risk of gastric cancer: epidemiologic evidence. *Cancer Sci* 2005;96:1–6.
30. Jeyaratnam J, Lee J, Lee HP, Phoon WO. Stomach cancer incidence in a cohort of fishermen in Singapore. *Scand J Work Environ Health* 1987;13:524–6.
31. Sasaki N, Takeda J, Fukushi S, Mitsuhashi T, Hijikata T, Fukushi M, Ishyama R. On the nutritional factors related to the geographical difference in the death rate from apoplexy in Japan. *Jpn J Public Health* 1960;7:1137–43.
32. Ozawa H. Geographic variation on mortality of cerebrovascular diseases and dietary life at the past time. *Jpn J Public Health* 1968;15:551–66.
33. National Institute of Health and Nutrition, Tokyo. Available at http://www.nih.go.jp/eiken/english/research/project_nhns.html (accessed in Nov. 2010).
34. Economic Planning Agency, Tokyo, Japan. Monthly consumer confidence survey, 1965. Data available in Japanese at http://www.esri.cao.go.jp/jp/stat/shouhi/quarter/0403fukyuritsu.xls (by the Economic and Social Research Institute, the Cabinet Office, The Government of Japan, accessed Oct 2011).
35. Yamaguchi N, Kakizoe T. Synergistic interaction between *Helicobacter pylori* gastritis and diet in gastric cancer. *Lancet Oncol* 2001;2:88–94.
36. Tanaka K, Kiyohara Y, Kubo M, Matsumoto T, Tanizaki Y, Okubo K, Ninomiya T, Oishi Y, Shikata K, Iida M. Secular trends in the incidence, mortality, and survival rate of gastric cancer in a general Japanese population: the Hisayama study. *Cancer Causes Control* 2005;16: 573–8.
37. Boffetta P, La Vecchia C. Neoplasms. In: Detels R, Beaglehole R, Lansang MA, Gulliford M, eds. Oxford textbook of public health, 5th edn. New York: Oxford University Press, 2009.
38. Oshima A, Hirata N, Ubukata T, Umeda K, Fujimoto I. Evaluation of a mass screening program for stomach cancer with a case-control study design. *Int J Cancer* 1986;38:829–33.
39. International Agency for Research in Cancer. Cancer incidence in five continents, vol.4. Lyon: IARC, 2007.
40. Ioka A. Cancer survival in Japan, using population-based cancer registry data. In: Ioka A, ed. Report by the research group for population-based cancer registry. Tokyo: Ministry of Health Labor and Welfare, 2011. 11–171.

J Epidemiol 2011;21(1):2-12
doi:10.2188/jea.JE20100090

Review Article

An Overview of Genetic Polymorphisms and Pancreatic Cancer Risk in Molecular Epidemiologic Studies

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Received June 9, 2010; accepted September 14, 2010; released online November 6, 2010

ABSTRACT

Background: Although pancreatic cancer has been extensively studied, few risk factors have been identified, and no validated biomarkers or screening tools exist for early detection in asymptomatic individuals. We present a broad overview of molecular epidemiologic studies that have addressed the relationship between pancreatic cancer risk and genetic polymorphisms in several candidate genes and suggest avenues for future research.
Methods: A comprehensive literature search was performed using the PubMed database.
Results: Overall, individual polymorphisms did not seem to confer great susceptibility to pancreatic cancer; however, interactions of polymorphisms in carcinogen-metabolizing genes, DNA repair genes, and folate-metabolizing genes with smoking, diet, and obesity were shown in some studies. The major problem with these studies is that, due to small sample sizes, they lack sufficient statistical power to explore gene–gene or gene–environment interactions. Another important challenge is that the measurement of environmental influence needs to be improved to better define gene–environment interaction. It is noteworthy that 2 recent genome-wide association studies of pancreatic cancer have reported that variants in ABO blood type and in 3 other chromosomal regions are associated with risk for this cancer, thus providing new insight into pancreatic cancer etiology.
Conclusions: As is the case in other complex diseases, common, low-risk variants in different genes may act collectively to confer susceptibility to pancreatic cancer in individuals with repeated environmental exposures, such as smoking and red meat intake. Clarification of gene–gene and gene–environmental interaction is therefore indispensable for future studies. To address these issues, a rigorously designed molecular epidemiologic study with a large sample is desirable.

Key words: pancreatic cancer; genetic polymorphisms; molecular epidemiology; gene–environment interaction

INTRODUCTION

Pancreatic cancer is a major cause of cancer mortality in developed countries.[1] In Japan, approximately 25 000 Japanese men and women died from pancreatic cancer in 2007, making it the fifth leading cause of cancer death.[2] Pancreatic cancer is a rapidly fatal disease, with mortality almost identical to incidence. The all-stage 5-year survival rate is less than 10%, the lowest among all cancer sites.[3]

The etiology of sporadic pancreatic cancer is not well understood. However, mounting evidence suggests that pancreatic carcinogenesis involves a complex interaction between genetic mutations, epigenetic alterations, and environmental risk factors.[4] Among these environmental risk factors, epidemiologic studies have identified only cigarette smoking and type II diabetes as clear risk factors for pancreatic cancer.[5,6] An association of pancreatic cancer with dietary habits remains unclear because of wide

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variation in dietary habits across populations and the difficulty of accurate diet measurement.[7]

Due to the completion of human genome sequencing and rapid progress in sequencing techniques, an increasing number of studies are exploring the associations between polymorphisms in candidate genes and pancreatic cancer risk. In a search of the PubMed database using the keywords "genetic polymorphism" plus "pancreatic cancer," we found 217 publications that had been published in the last 10 years. Furthermore, a small but growing body of research has addressed gene–environment interaction contributing to pancreatic cancer development.[8–10] Of special importance are 2 recent genome-wide association studies (GWAS), which reported that a variant in ABO blood type and 3 other variants in chromosomal regions are associated with pancreatic cancer risk.[11,12]

An estimated 10% of pancreatic cancer cases are associated with inherited predisposition, based on familial clustering.[13] Several germline mutations have been linked to familial pancreatic cancer.[14] The role of germline mutations in several genes, such as *INK4A*, *BRCA2*, and *LKB1*, and their associations with pancreatic cancer risk is beyond the scope of this review. However, in this article we provide a broad overview of molecular epidemiologic studies that have investigated the relationship between genetic polymorphisms in several candidate genes and their interactions with environmental factors in conferring pancreatic cancer risk. We focus on polymorphisms in carcinogen-metabolizing genes, DNA repair genes, and folate-metabolizing genes because the functional importance of these genes has been elucidated and because most published studies have examined these genes. Furthermore, on the basis of findings from GWAS and biomarker, epidemiologic, and experimental studies, we identify additional genetic polymorphisms that require analysis due to their potentially important role in the etiology of pancreatic cancer.

METHODS

We performed a comprehensive literature search using the PubMed database. The keywords used were "genetic polymorphism" plus "pancreatic cancer." In addition, we also cite the published literature addressing candidate gene polymorphisms and their associations with other cancer types, as well as findings from GWAS and experimental studies.

RESULTS

Tobacco smoking and genetic polymorphisms in carcinogen-metabolizing genes

Pancreatic cancer is a tobacco-induced cancer: epidemiologic studies have consistently shown that cigarette smoking increases the risk for pancreatic cancer. A meta-analysis of 82 case–control and cohort studies reported a 1.8-fold increased risk for current smokers as compared with nonsmokers.[5] Tobacco smoke contains a variety of carcinogens, of which 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone and its metabolite 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol are the major carcinogens involved in pancreatic carcinogenesis.[15] While the role of polycyclic aromatic hydrocarbons exposure and metabolism in pancreatic cancer needs further investigation, aromatic amine and heterocyclic amine have been implicated in the pathogenesis of pancreatic cancer.[16]

Metabolic activation of carcinogens forms DNA adducts, causing mutations in crucial genes, including *RAS*, *MYC*, *TP53*, and *P16*.[15] The accumulation of these genetic mutations leads to uncontrolled cell growth and tumor development. Enzymes such as cytochrome P450S, glutathione-S-transferase (GST), N-acetyltransferase 1 (NAT1), and N-acetyltransferase (NAT2) are involved in the metabolic activation of carcinogens to DNA adducts and in detoxification to other products.[17] Human cytochrome P450 1A1 (*CYP1A1*) encodes aryl hydrocarbon hydroxylase, a phase I enzyme involved in the activation of tobacco-related carcinogens.[17] The GSTs are a family of phase II isoenzymes that are involved in phase II drug metabolism by conjugation of electrophilic substances with glutathione.[18] GST detoxifies a broad range of substances, including carcinogens, environmental toxins, and drugs. Genetic polymorphisms resulting in lack of enzyme activity due to homozygous deletion of the *GSTM1* and *GSTT1* genes have been described.[18] The frequencies of these deletions vary across populations.[19] Molecular epidemiologic studies have shown increased risk for various cancers among individuals with the *NAT1* rapid acetylator or *NAT2* slow acetylator genotypes, in the presence of known carcinogen exposure, such as smoking or dietary exposure to heterocyclic amine.[20]

Although several molecular epidemiologic studies have examined the associations between variants of the genes encoding *CYP*, *GST*, and *NAT* enzymes and pancreatic cancer risk, most of the important findings regarding the main effects of genetic variations or gene–environment interactions were reported by 2 case–control studies: an ongoing hospital-based case–control study at MD Anderson Cancer Center[21] and a population-based case–control study in 6 areas of San Francisco Bay from 1994 to 2001[8] (Table 1). Both studies enrolled a relatively large number of case and control subjects, which allowed for an analysis of gene–environment interactions. The case–control study conducted at MD Anderson Cancer Center revealed the following. (1) *NAT1* rapid alleles were associated with 1.5-fold increased risk, and the effect was more prominent among ever smokers and females.[21] A significant synergistic effect of the *CYP1A2**1F allele and *NAT1* rapid alleles with respect to the risk for pancreatic cancer was also detected. (2) The rare *NAT1*10* or *NAT1*11-NAT2*6A* diplotype may be an "at-risk" genetic variant for pancreatic cancer.[22] (3) The *GSTP1*C* variant conferred a possible protective effect against pancreatic cancer.[23] (4) A significant interaction was noted between *CYP1A2*, *NAT1*, and heavy smoking and dietary mutagen intake.[24]

In the population-based case–control study carried out in 6 areas of San Francisco Bay, Duell et al examined polymorphisms in carcinogen-metabolizing genes, smoking, and pancreatic cancer risk in whites and found that there was no significant increase in risk associated with any genotype examined.[8] However, the odds ratio (OR) was 5.0 (95% confidence interval [CI], 1.8–14.5) for heavy smokers who had a deletion polymorphism in *GSTT1*, suggesting that inherited deletion polymorphisms in *GSTT1* increase susceptibility to smoking-related pancreatic cancer. Another notable finding from this study was that the interaction was stronger in women than in men. Although these results require replication in other studies, the findings suggest that women with a *GSTT1*-null or *GSTM1*-null genotype may be more susceptible than men to the effects of DNA adducts. In addition to the 2 studies mentioned above, other, small studies have addressed this issue, although the findings are difficult to interpret due to the small sample size.[25–27]

More studies are needed to examine genetic variations in tobacco-metabolizing genes and their associations with pancreatic cancer among different ethnic populations. However, based on current, limited evidence from molecular epidemiologic studies, it seems unlikely that individual polymorphisms themselves confer major susceptibility to pancreatic cancer. Given the reported synergistic effects of smoking and certain carcinogen-metabolizing gene polymorphisms, it is essential to clarify gene–environment interactions in future studies.

DNA repair and polymorphisms in DNA repair genes

DNA repair plays a crucial role in cellular defense against mutations caused by carcinogens and endogenous mechanisms. Four types of DNA repair systems—nucleotide excision repair, base excision repair (BER), mismatch repair, and recombination repair—have been identified so far.[28] Defects in these pathways may result in a predisposition to cancer. Each type of DNA repair is understood in considerable detail. We focus on BER because the genetic polymorphisms in this repair pathway are the most extensively studied in

Table 1. Summary of findings from case–control studies of genetic polymorphisms in carcinogen-metabolizing genes and their interactions with environmental factors and pancreatic cancer risk

Study and year	Study population	No. of cases	No. of controls	Genetic polymorphisms	Main effects of polymorphisms	Gene–environment interaction
Lee et al, 1997 (Ref 27)	Koreans	45	53	P-450 (1A1, 2D6, and 2E1)	No association	Unreported
Bartsch H, et al, 1998 (Ref 25)	Whites	81	78	NAT1, NAT2, GSTM1, NAD(P)H: NQO1	GSTM1 and NAT1 enzymes associated with modest increase in susceptibility to pancreatic cancer	Unreported
Liu et al, 2000 (Ref 26)	Canadian	149	146	CYP1A1, GSTM1, GSTT1	No association	Not observed
Duell EJ, et al, 2002 (Ref 8)	Whites	309	964	CYP1A1, GSTM1, GSTT1	No significant main effects	Never smokers with GSTT1-present genotype vs heavy smokers with GSTT1-null genotype: OR, 3.2 (95% CI, 1.3–8.1) for men and 5.0 (1.8–14.5) for women
Li et al (Ref 21)	Non-Hispanic whites	365	379	P4501A1, NAT	NAT1 rapid alleles associated with 1.5-fold increased risk	Interaction with smoking
Jiao et al, 2007 (Ref 22)	Non-Hispanic whites	352	315	GSTM1, GSTT1, GSTP1	No significant main effects	GSTP1*C variant conferred possible protective effect in older subjects
Jiao et al, 2007 (Ref 23)	Non-Hispanic whites	532	581	Haplotype of NAT1 and NAT2	Rare NAT1*10 or NAT*11-NAT2*6A diplotype associated with increased risk	Interactions between NAT2 slow genotype and smoking and history of diabetes
Suzuki et al, 2008 (Ref 24)	Non-Hispanic whites	755	636	P4501A2, SULT1A1, and NAT	No significant main effects	Interactions between CYP1A2, NAT1, and heavy smoking and dietary mutagen intake

Abbreviations: NAT, N-acetyltransferase; GSTM, glutathione-S-transferase; CYP1A1, cytochrome P450 1A1; OR, odds ratio; CI, confidence interval.
Results reported by Li et al, Jiao et al, and Suzuki et al came from the same research group.

molecular epidemiologic studies. DNA bases are particularly susceptible to oxidation mediated by reactive oxygen species, which can be produced as a consequence of ionizing radiation or environmental exposure to transition metals, chemical oxidants, and free radicals. Reactive oxygen species have been linked to the initiation and progression of cancer.[29] BER plays an important role in preventing mutations associated with a common product of oxidative damage to DNA, 8-oxoguanine. X-Ray Repair Cross-Complementing Group 1 (*XRCC1*), located on 19q13.2, is a polymorphic BER gene that has been the most extensively examined in molecular epidemiologic studies of the risk of various cancers.[30] In the above-mentioned population-based case–control study conducted in 6 areas of San Francisco Bay,[31] a synergistic effect between the *XRCC1 399*Gln allele and tobacco smoking in relation to pancreatic cancer risk was observed, although no significant associations were noted between *XRCC1* genotypes and pancreatic cancer risk. As compared with never-active smokers and passive smokers with the Arg/Arg genotype, the age- and race-adjusted ORs for heavy smokers (≥41 pack-years) with the Gln/Gln or Arg/Gln genotypes were 7.0 (95% CI, 2.4–21) in women and 2.4 (1.1–5.0) in men. The interaction suggests that *XRCC1* Arg399Gln and BER capacity are important in susceptibility to smoking-induced pancreatic cancer. However, these findings need to be confirmed in other studies, as the number of study subjects was small in the analysis exploring gene–environment interaction.

The 8-oxoguanine DNA glycosylase (*OGG1*) gene is another BER gene that removes oxidative DNA lesions.[28] *OGG1* has been associated with altered risk of human cancers. In data from the hospital case–control study conducted at MD Anderson Center in the United States, Li et al noted significantly reduced overall survival in patients with the *OGG1* C315G (rs1052133) GG homozygous variant genotype.[32] Furthermore, they reported a weak interaction of the *OGG1* C315G CC/CG genotype with diabetes in pancreatic cancer. These findings suggest that the CC/CG genotype, combined with environmental exposure, confers increased susceptibility to pancreatic cancer.

Li et al also examined associations of pancreatic cancer with selected DNA repair polymorphisms in other types of DNA repair pathways, including *XRCC2, XRCC3*,[33] *RAD54L*, and *RecQ1* in the recombination repair pathway,[34] and the xeroderma pigmentosum group D (*XPD*) in the NER pathway.[35] They found that variant alleles of *XRCC2* R188H and *XRCC3* A17893G were associated with significantly reduced survival in pancreatic cancer patients and that *XRCC2* Arg188His polymorphisms may be genetic modifiers for smoking-related pancreatic cancer.

Overall, evidence from a small number of molecular epidemiologic studies supports a role for genetic variability in DNA repair in the risk for pancreatic cancer. Due to small sample sizes and heterogeneous study designs, however, the results are inconclusive and require confirmation. Because hundreds of genetic polymorphisms may be involved in maintaining genomic integrity, additional studies with large sample sizes are needed to elucidate multiple sequence variants in a gene or multiple genes within an entire pathway.

Folate intake and polymorphisms in folate-metabolizing genes

Folate is a water-soluble B vitamin abundant in green leafy vegetables, citrus fruit, legumes, and cereals. Substantial evidence from epidemiologic and laboratory research supports a role for folate in carcinogenesis.[36,37] Epidemiologic studies have consistently shown an inverse association between folate intake and pancreatic cancer risk. Based on a meta-analysis in which data from 4 cohort studies and 1 case–control study were analyzed, individuals with the highest folate intake had a 51% lower risk than those with the lowest folate intake.[38] Mechanistic studies have elucidated 2 major underlying mechanisms that may be involved. Folate deficiency may induce misincorporation of uracil into DNA, leading to chromosomal breaks and mutations. In addition, folate deficiency may cause aberrant DNA methylation, resulting in altered expression of critical proto-oncogenes and tumor suppressor genes.[39] Moreover, functional polymorphisms in folate-metabolizing genes may confer susceptibility to cancer. Among the several polymorphisms in the folate metabolic pathway, polymorphisms in the 5-10 methylenetetrahydrofolate reductase (*MTHFR*) gene are the most extensively studied. A central enzyme in folate metabolism, MTHFR irreversibly converts 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, the predominant form of folate in systemic circulation. Thus, *MTHFR* acts as a critical junction in folate metabolism by directing folate metabolites toward the DNA methylation pathway and away from the DNA synthesis pathway. Two common functional polymorphisms of the *MTHFR* gene, C677T and A1298C, have been identified.[39] Regarding C677T, the TT genotype (variant type) has been shown to have 35% lower enzyme activity than the CC genotype (wild type).[39] As for A1298C, homozygotes (CC) have approximately 60% of normal *MTHFR* activity.

Since 2005, five studies have reported an association between the *MTHFR* C677T genotype and pancreatic cancer risk, but the results were not consistent[9,40–43] (Table 2). The TT genotype was associated with significantly increased risk for pancreatic cancer in 2 case–control studies carried out in the United States[9] and China[40]: the ORs were 2.14 (95% CI, 1.14–4.01) and 5.12 (2.94–9.10), respectively. Notably, a significant interaction between TT genotype and smoking in pancreatic cancer risk was also observed. In these 2 studies, heavy smokers with the TT genotype had an approximately 7-fold increased risk as compared with nonsmokers with the CC genotype.[9,40] In contrast, 2 Japanese case–control studies reported no increased risk associated with the TT genotype.[41,42] In one of these studies, the OR for pancreatic cancer in individuals with the TT genotype was 0.75 (0.41–1.35), but the association was statistically insignificant.[42] Due to the small number of studies and the wide heterogeneity in results, a summary OR could not be calculated in a meta-analysis of the *MTHFR* C677T genotype and pancreatic cancer risk, as only 3 published studies were included.[38] Inadequate sample size and different criteria for control selection might have contributed to the inconsistent results reported so far. As for the A1298C genotype, evidence is insufficient to draw a conclusion: 2 studies showed no important effects on pancreatic cancer, and one study suggested a 1.8-fold increased risk in subjects with the CC genotype.[38]

Given the strong interaction of the *MTHFR* genotype with environmental factors such as smoking and alcohol consumption, it is important to unravel their complex relationships in additional large, adequately powered studies. Furthermore, because the balance between the use of methylenetetrahydrofolate for DNA synthesis rather than for methionine synthesis might depend on the presence of the 677T variant of *MTHFR* and nutritional folate status, studies targeting populations with folate deficiency in developing countries may provide valuable information.

Table 2. Summary of findings from case–control studies of genetic polymorphisms in folate-metabolizing genes and their interactions with environmental factors and pancreatic cancer risk

Study and year	Study population	No. of cases	No. of controls	Genetic polymorphisms	Main effects of polymorphisms[a]	Gene–environment interaction[a]
Li et al, 2005 (Ref 9)	Non-Hispanic US whites	347	348	*MTHFR* C677T, A1298C	Significant effect for C677T: CT, 0.90 (0.63–1.27), TT, 2.14 (1.14–4.01); no association for A1298C	Heavy smokers with TT vs never smokers with CC/CT: 6.83 (1.91–24.38) Heavy alcohol drinkers with TT vs nondrinkers with CC/CT: 4.23 (0.88–20.3)
Wang et al, 2005 (Ref 40)	Chinese	163	337	*MTHFR* C677T, A1298C, TS	Significant effect for C677T: CT, 2.60 (1.61–4.29), TT, 5.12 (2.94–9.10); no association for A1298C	Heavy smokers with TT vs never smokers with CC/CT: 6.69 (3.39–13.63) Alcohol drinkers with TT/CT vs nondrinkers with CC: 4.39 (2.25–8.78)
Matsubayashi et al, 2005 (Ref 41)	Americans	303	305	*MTHFR* C677T, A1298C	No association for C677T: CT, 0.79 (0.56–1.11), TT, 1.10 (0.67–1.82)	No significant interaction with smoking
Suzuki et al, 2008 (Ref 42)	Japanese	157	785	*MTHFR* C677T, MTR A2756G, TS variable number of tandem repeat	No association for C677T: CT, 0.98 (0.65–1.47), TT, 0.75 (0.41–1.35)	No significant interaction with alcohol drinking
Ohnami et al, 2008 (Ref 43)	Japanese	198	182	*MTHFRC677T*, MTRR (rs1801394, rs162049, rs10380)	No association for C677T, but MTRR polymorphisms associated with increased risk	No association

Abbreviations: MTHFR, methylenetetrahydrofolate reductase; MTR, methionine synthase; MTRR, methionine synthase reductase; OR, odds ratio.
[a]Values are odds ratios (95% confidence interval).

Table 3. Associations of genetic polymorphisms and pancreatic cancer risk that require assessment in future studies

Candidate genes	Selected polymorphisms	Potential interactions with environmental factors	Circulating biomarker
Vitamin D signaling	rs11574143	Sun exposure, diet	Plasma 25-hydroxyvitamin D
Melatonin receptors and clock genes	*MTNR1B*, rs10830963, rs11133373 in *CLOCK*	Diabetes	Plasma or urinary melatonin (6-sulfatoxymelatonin)
Insulin, IGF gene	IGF1 haplotype and the IGF2 Ex4 -233 C>T TT genotype	Diabetes, obesity	Plasma or serum IGF
TGF-β signaling	*TGFBR1**6A	Diabetes	Plasma or serum TGF-β
Infection-related gene polymorphisms	COX-2 polymorphisms	N/A	N/A
ABO gene	rs505922	N/A	N/A
Genes in chromosome 13q22.1	Novel polymorphisms to be identified	N/A	N/A

Abbreviations: IGF, insulin-like growth factor; TGF-β, transforming growth factor-β; MTNR1B, melatonin receptor 1B; COX-2, cyclooxygenase-2. N/A: not applicable.

Alcohol consumption and polymorphisms in alcohol-metabolizing enzymes

Although the majority of prospective cohort studies found no significant increase in the risk of pancreatic cancer with moderate to high levels of alcohol intake in a general population,[7] some evidence suggests that excessive drinking may increase risk in population subsets.[44]

Ethanol is mainly metabolized to acetaldehyde by alcohol dehydrogenase enzymes and further oxidized to acetate by acetaldehyde dehydrogenase. Acetaldehyde has been shown to have carcinogenic effects in experimental studies and is the main mechanism to explain alcohol-induced carcinogenesis.[45] Variations in the production and/or oxidation of acetaldehyde among individuals are caused by single-nucleotide polymorphisms (SNPs) of *ADH1B, ADH1CI,* and *ALDH2*.[45] In particular, people homozygous for *ALDH2**2 display flush syndrome, which is characterized by nausea, vomiting, and facial flushing after ingestion of a small amount of alcohol.

Very few studies have addressed the role of polymorphisms in alcohol-metabolizing enzymes and pancreatic cancer risk. A recent case–control study involving 160 pancreatic cancer patients and 800 age- and sex-matched controls in Japan found that alcohol consumption was associated with increased risk in individuals with the *ALDH2* Lys+ allele or *ADH1B* His/His or *ADH1C* Arg/Arg genotypes, but not in those with the *ALDH2* Glu/Glu genotype or *ADH1B* Arg or *ADH1C* Gln alleles.[46] This suggests that the risk of pancreatic cancer is associated with the combined effect of alcohol consumption and certain polymorphisms in alcohol-metabolizing enzymes.

Because the metabolism of alcohol and acetaldehyde is strongly influenced by alcohol-metabolizing enzymes, future molecular epidemiologic studies need to examine the effect of these polymorphisms on pancreatic cancer risk while accounting for alcohol consumption.

Vitamin D and polymorphisms in vitamin D pathway genes

Humans get vitamin D mainly from exposure to sunlight or their diet. Vitamin D is metabolized in the liver to 25-hydroxyvitamin D [25(OH)D], which is further metabolized in the kidneys by the enzyme 25-hydroxivitamin D-1α-hydroxylase (CYP27B1) to its active form, 1,25-dihydroxyvitamin D.[47] Vitamin D receptor, a crucial mediator of the cellular effects of vitamin D, is present in a variety of cell types, including pancreatic beta cells.[48] Experimental evidence shows that vitamin D receptor interacts with other cell-signaling pathways to influence cancer development.[49] Ecologic studies have linked sun exposure to lower pancreatic cancer mortality.[50] Individuals with higher circulating 25(OH)D levels have been found to have decreased risks of breast, colorectal, and prostate cancer in numerous prospective studies.[51] Given the collective evidence from epidemiologic and experimental studies, it is plausible that high vitamin D levels may be associated with a lower risk of pancreatic cancer. However, the role of vitamin D in the development of pancreatic cancer remains unclear due to the small number of studies.

High vitamin D exposure is hypothesized to decrease cancer risk, possibly through genomic effects modulated by the vitamin D receptor, and by autocrine/paracrine metabolism of the vitamin D receptor's ligand, 1α,25-(OH)2-vitamin D3.[49] Recently, an increasing number of studies have examined polymorphisms in vitamin D receptor and selected genes in the vitamin D pathway in relation to colorectal, breast, and prostate cancer risk.[48] However, there is currently no strong, consistent epidemiologic evidence for a substantial influence of any single variant in vitamin D pathway genes on cancer risk. The association of pancreatic cancer with serum vitamin 25(OH)D levels and polymorphic variants in genes encoding for enzymes that synthesize, carry, and degrade vitamin D is an important research subject for future studies.

Circadian disruption, melatonin, and genetic variations in clock genes

To date, no studies have examined the association between circadian disruption and pancreatic cancer risk in humans. Experimental data, however, have shown that disruption of circadian rhythms in mice is associated with accelerated growth of pancreatic cancer.[52] Although the findings are not entirely consistent, epidemiologic studies have indicated that shift work is significantly associated with increased risks of breast, colorectal, and prostate cancer.[53] On the basis of considerable evidence from animal studies and limited evidence from epidemiologic studies, the working group of IARC concluded in 2007 that "shift-work that involves circadian disruption is probably carcinogenic to humans."[54] The principal mechanism involves melatonin, a neurohormone that regulates the circadian rhythm.[55] Three recent GWAS have shown that the common variant *MTNR1B* (melatonin receptor 1B) is associated with insulin and glucose concentrations.[56–58] The melatonin receptor MT1 is highly expressed in pancreatic islet cells, and the expression of *MTNR1B* has been confirmed in both islets and sorted beta cells.[59] Given the close relationship of hyperinsulinemia and diabetes with pancreatic cancer risk, it might prove interesting to examine the risk genotypes of *MTNR1B* and their interactions with diabetes and other environmental factors in pancreatic cancer development.

In addition to melatonin, circadian rhythms are controlled and maintained by several circadian genes via transcription–translation feedback loops that include positive activators, such as Clock, neuronal PAS domain protein 2 (*NPAS2*), cryptochrome 1 (*CRY1*) and *CRY2*, and period 1 (*PER1*), *PER2*, and *PER3*.[60] To test the hypothesis that genetic variations in these genes may confer susceptibility to prostate cancer, Zhu et al genotyped a total of 41 tagging and amino acid-altering SNPs in 10 circadian genes in a population-based case–control study of white men and found that *NPAS2* showed the most robust association with prostate cancer risk.[61] No studies, however, have examined genetic polymorphisms in clock genes and pancreatic cancer risk.

Because of the important role of melatonin and circadian genes in maintaining circadian rhythm, future studies may address genetic variations in these genes and the risk of pancreatic cancer.

Insulin and insulin-like growth factor gene polymorphisms

Obesity and type II diabetes are well established risk factors for pancreatic cancer, especially in developed countries. Elevated levels of insulin and insulin-like growth factors (IGFs), such as IGF-I, are important mechanisms underlying the association between obesity, diabetes, and pancreatic cancer.[62] Insulin, IGF-1, and the insulin receptor-related receptor can form functional hybrids.[63] IGF1 and IGF1 receptors are highly expressed in pancreatic cancer cells, and IGF2 imprinting is disrupted in many tumors.[64]

Despite strong experimental evidence indicating that IGFs play an important role in carcinogenesis—including the regulation of cell proliferation, differentiation, and apoptosis—the results of epidemiologic studies examining IGFs in relation to cancer risk are less persuasive. Using data from a nested case–control study in the Japan Collaborative Cohort (JACC) Study, we found a positive association between baseline IGF-1 levels and the risk of pancreatic cancer mortality in apparently healthy Japanese.[65] However, no significant associations were observed in other studies.[66] Only 1 study has examined the association between genetic polymorphisms in IGF genes and pancreatic cancer risk.[67] Of 6 SNPs of IGF1 and IGF2 that were examined in a case–control study by Suzuki et al, the IGF1 haplotype and the IGF2 Ex4 -233 C>T TT genotype were significantly associated with decreased risk of pancreatic cancer, which suggests that polymorphic variants of the IGF genes may serve as a susceptibility factor for pancreatic cancer. Future studies are warranted to explore polymorphisms in IGF gene pathways and their interaction with obesity and physical activity in pancreatic cancer risk.

Transforming growth factor-β (TGF-β) and polymorphisms in the TGF-β pathway

TGF-β regulates tumor initiation, progression, and metastasis via its signaling pathway involving membrane receptors and SMAD transcription factors.[68] The dual role of TGF-β in cancer, both as a tumor suppressor and tumor promoter, has been well defined.[69] Several lines of evidence demonstrate that pancreatic cancer is clearly linked to TGF-β.[70] In particular, SMAD4, a component of the TGF-β pathway, is mutated in approximately 50% of pancreatic cancers.[71]

Because of the presence of plausible mechanisms, a study of the associations of polymorphisms in TGF-β pathway with pancreatic cancer risk should prove interesting. *TGFBR1*6A* is emerging as a high frequency, low-penetrance tumor susceptibility allele that confers susceptibility to breast, ovarian, and colorectal cancer. A meta-analysis of 7 case–control studies of *TGFBR1*6A* and various cancer types combined showed that *TGFBR1*6A* carriers had a 26% increased risk.[72] The role of *TGFBR1*6A* in pancreatic cancer remains unclear and is a subject of future study.

Inflammation and infection-related gene polymorphisms

Inflammation has been implicated in pancreatic carcinogenesis. Cyclooxygenase-2 (COX2) is a key enzyme involved in biologic processes including inflammation, immune function, and cell proliferation.[73] The overexpression of this enzyme has been shown in pancreatic cancer.[74] However, there have been few studies addressing inflammation-related genetic polymorphisms and pancreatic cancer risk. Zhao et al showed that functional *COX-2* polymorphisms are associated with susceptibility to pancreatic cancer.[75] In another case–control study, 3 infection-related polymorphisms (*TNF-A, RANTES, and CCR5*) were examined, but no significant effects were found.[76]

Helicobacter pylori infection induces chronic inflammation and has been established as a risk factor for gastric cancer. It remains controversial, however, whether *H. pylori* infection plays a role in pancreatic cancer development.[77] Epidemiologic studies examining this issue have produced mixed results. The hypothesis has been proposed that polymorphisms in genes involved in inflammatory response, such as *IL-1A, IL-1B, IL-6, IL-8*, may help explain why only a subset of individuals infected with *H. pylori* develops gastric cancer. Similarly, it is important to comprehensively analyze the effects of these polymorphisms on pancreatic cancer risk.

SNPs indentified by genome-wide association studies

Genome-wide association studies (GWAS) have been proven to be a valuable tool for identifying common alleles that influence disease risk.[78] Fast-evolving sequencing technology allows researchers to scan across the genome in a large set of cases and controls to identify new associations that link certain regions to disease risk.

The first GWAS for pancreatic cancer, published in *Nature Genetics* in August 2009, identified common risk variants that map to the first intron of the *ABO* gene on chromosome 9q34.2 (SNP rs505922).[11] This finding implies that people with blood group O may have a lower risk than those with groups A or B.

Base on DNA collected from nearly 4000 patients in 13 different studies, a second GWAS for pancreatic cancer has, for the first time, identified pancreatic cancer susceptibility loci on 3 chromosomes—13q22.1, 1q32.1, and 5p15.33.[12] Of the 3 regions, the locus on 13q22.1 appears to be specific for pancreatic cancer.

Findings from the 2 GWAS of pancreatic cancer have provided new insight into pancreatic cancer etiology; however, they need to be replicated in other large studies. Furthermore, follow-up studies after the GWAS must address whether SNPs discovered by GWAS represent functional variants or simply tag true variants located in the same haplotype.

Mitochondrial genetic polymorphisms

Mitochondria play an important role in cellular energy metabolism, free radical generation, and apoptosis. Mitochondrial DNA mutations can initiate a cascade of events leading to persistent oxidative stress, a condition that probably favors tumor development.[80] Although previous studies have examined the association between mitochondrial genetic polymorphisms and pancreatic cancer,[81–83] the results were inconsistent. While a mitochondrial SNP in the 16519 mitochondrial DNA nucleotide was found to be associated with worse prognosis,[81] this positive association was not replicated in a recent study involving 990 pancreatic cancer patients.[82] A recent large case–control study comprised 955 participants with primary pancreatic adenocarcinoma and 1102 control subjects and examined 24 mitochondrial SNPs and 11 common haplogroups, none of which was significantly associated with pancreatic cancer risk.[83] Their results did not support the significant involvement of mitochondrial SNPs or haplogroups in the development of pancreatic cancer. Because of the important role of mitochondrial DNA in cancer, further investigations of mitochondrial genetic variations are necessary to provide insight into the etiology of pancreatic cancer.

DISCUSSION

Molecular epidemiologic studies examining the associations between polymorphisms in several gene pathways and pancreatic cancer risk have produced mixed results. Overall, individual polymorphisms did not seem to confer marked susceptibility; however, some studies implicated interactions of polymorphisms in carcinogen-metabolizing genes, DNA repair genes, and folate-metabolizing genes with smoking, diet, and obesity. The principal weakness of these studies is small sample size; thus, it is difficult to detect statistically significant gene–gene or gene–environment interactions. Because of this, no functional variants reported so far have been used to predict pancreatic cancer risk in the clinical setting. Another critical challenge is that the measurement of environmental influence in epidemiologic studies must be improved to better define gene–environment interaction.

Two recent GWAS of pancreatic cancer have provided intriguing results that need to be confirmed in additional studies. With the decreasing cost of genotype sequencing, we expect that future GWAS will unravel causal variants with significant effects on pancreatic cancer. Hopefully, disease susceptibility variants will be discovered from GWAS, and the interactions of these variants with environmental factors will be more frequently confirmed in molecular epidemiologic studies. Since we have yet to discover rare variants that greatly increase the risk of pancreatic cancer, perhaps, as is the case with other complex diseases, common low-risk variants in different genes act collectively to confer susceptibility to pancreatic cancer in individuals who have repeated environmental exposures, such as smoking and intake of red meat. A recent study provided critical evidence to support this notion by demonstrating that pancreatic cancer results from genetic alterations of a large number of genes that function through 12 pathways and processes,[79] including TGF-β signaling and DNA damage control, which were discussed in this review.

What is the future direction for research on the etiology of pancreatic cancer? First, we believe that unraveling the functional SNP variants in a number of identified gene pathways, combined with novel variants identified in GWAS, is essential in deepening our understanding of pancreatic cancer risk. To achieve this goal, the complex gene–gene and gene–environmental interactions must be clarified in a rigorously designed molecular epidemiologic study with a large sample size. Second, in addition to SNPs, there is increasing recognition of the role of genetic variations—such as DNA copy number variations and variable-number tandem repeats—in cancer predisposition.[84] High-resolution SNP arrays have made it possible to identify copy number variations. Moreover, there have been studies linking copy number variations and variable-number tandem repeats to pancreatic cancer risk.[85,86] Elucidating these associations is an important goal for future research.

ACKNOWLEDGMENTS

This work was supported by Grant-in-Aid for Cancer Research (21Shi-11-1) from the Ministry of Health, Labour and Welfare, Japan.

Conflicts of interest: None declared.

REFERENCES

1. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. CA Cancer J Clin. 2005;55:74–108.
2. Foundation for Promotion of Cancer Research. Cancer Statistics in Japan-2008.
3. Matsuno S, Egawa S, Fukuyama S, Motoi F, Sunamura M, Isaji S, et al. Pancreatic cancer registry in Japan: 20 years of experience. Pancreas. 2004;28:219–30.
4. Bardeesy N, DePinho RA. Pancreatic cancer biology and genetics. Nat Rev Cancer. 2002;2:897–909.
5. Iodice S, Gandini S, Maisonneuve P, Lowenfels AB. Tobacco and the risk of pancreatic cancer: a review and meta-analysis. Langenbecks Arch Surg. 2008;393:535–45.
6. Huxley R, Ansary-Moghaddam A, Berrington de González A, Barzi F, Woodward M. Type-II diabetes and pancreatic cancer: a meta-analysis of 36 studies. Br J Cancer. 2005;92:2076–83.
7. Michaud DS. Epidemiology of pancreatic cancer. Minerva Chir. 2004;59:99–111.
8. Duell EJ, Holly EA, Bracci PM, Liu M, Wiencke JK, Kelsey KT. A population-based case–control study of polymorphisms in carcinogen-metabolizing genes, smoking, and pancreatic adenocarcinoma risk. J Natl Cancer Inst. 2002;94:297–306.
9. Li D, Ahmed M, Li Y, Jiao L, Chou TH, Wolff RA, et al. 5,10-Methylenetetrahydrofolate reductase polymorphisms and the risk of pancreatic cancer. Cancer Epidemiol Biomarkers Prev. 2005;14:1470–6.
10. McWilliams RR, Bamlet WR, Cunningham JM, Goode EL, de Andrade M, Boardman LA, et al. Polymorphisms in DNA repair genes, smoking, and pancreatic adenocarcinoma risk. Cancer Res. 2008;68:4928–35.
11. Amundadottir L, Kraft P, Stolzenberg-Solomon RZ, Fuchs CS, Petersen GM, Arslan AA, et al. Genome-wide association study identifies variants in the ABO locus associated with susceptibility to pancreatic cancer. Nat Genet. 2009;41:986–90.
12. Petersen GM, Amundadottir L, Fuchs CS, Kraft P, Stolzenberg-Solomon RZ, Jacobs KB, et al. A genome-wide association study identifies pancreatic cancer susceptibility loci on chromosomes 13q22.1, 1q32.1, 5p15.33. Nat Genet. 2010;42:224–8.
13. Schenk M, Schwartz AG, O'Neal E, Kinnard M, Greenson JK, Fryzek JP, et al. Familial risk of pancreatic cancer. J Natl Cancer Inst. 2001;93:640–4.
14. Hezel AF, Kimmelman AC, Stanger BZ, Bardeesy N, Depinho RA. Genetics and biology of pancreatic ductal adenocarcinoma. Genes Dev. 2006;20:1218–49.
15. Hecht SS. Tobacco carcinogens, their biomarkers and tobacco-related cancer. Nat Rev Cancer. 2003;3:733–44.
16. Thompson PA, Seyedi F, Lang NP, MacLeod SL, Wogan GN, Anderson KE, et al. Comparison of DNA adduct levels associated with exogenous and endogenous exposures in human pancreas in relation to metabolic genotype. Mutat Res. 1999;424:263–74.
17. Nebert DW, Dalton TP. The role of cytochrome P450 enzymes in endogenous signaling pathways and environmental carcinogenesis. Nat Rev Cancer. 2006;6:947–60.
18. Rebbeck TR. Molecular epidemiology of the human glutathione S-transferase genotypes GSTM1 and GSTT1 in cancer susceptibility. Cancer Epidemiol Biomarkers Prev. 1997;6:733–43.
19. Geisler SA, Olshan AF. GSTM1, GSTT1, and the risk of squamous cell carcinoma Lin 30 of the head and neck: a mini-HuGE review. Am J Epidemiol. 2001;154:95–105.
20. Hein DW, Doll MA, Fretland AJ, Leff MA, Webb SJ, Xiao GH, et al. Molecular genetics and epidemiology of the NAT1 and NAT2 acetylation polymorphisms. Cancer Epidemiol Biomarkers Prev. 2000;9:29–42.
21. Li D, Jiao L, Li Y, Doll MA, Hein DW, Bondy ML, et al. Polymorphisms of cytochome P4501A2 and N-acetyltransferase genes, smoking and risk of pancreatic cancer. Carcinogenesis. 2006;27:103–11.
22. Jiao L, Doll MA, Hein DW, Bondy ML, Hassan MM, Hixson JE, et al. Haplotype of N-Acetyltransferase 1 and 2 and risk of pancreatic cancer. Cancer Epidemiol Biomarkers Prev. 2007;16:2379–86.
23. Jiao L, Bondy ML, Hassan MM, Chang DZ, Abbruzzese JL, Evans DB, et al. Glutathione S-transferase gene polymorphisms and risk and survival of pancreatic cancer. Cancer. 2007;109:840–8.
24. Suzuki H, Morris JS, Li Y, Doll MA, Hein DW, Liu J, et al. Interaction of the cytochrome P4501A2, SULT1A1 and NAT gene polymorphism with smoking and dietary mutagen intake in modification of the risk of pancreatic cancer. Carcinogenesis. 2008;29:1184–91.
25. Bartsch H, Nair U, Risch A, Rojas M, Wikman H, Alexandrov K. Genetic polymorphisms of CYP genes, alone or in combination, as a risk modifier of tobacco-related cancers. Cancer Epidemiol Biomarkers Prev. 2000;9:3–28.
26. Liu G, Ghadirian P, Vesprini D, Hamel N, Paradis AJ, Lal G, et al. Polymorphisms in GSTM1, GSTT1, and CYP1A1 and risk of pancreatic adenocarcinoma. Br J Cancer. 2000;82:1646–9.
27. Lee HC, Yoon YB, Kim CY. Association between genetic polymorphisms of the cytochromes P-450 (1A1, 2D6, and 2E1) and the susceptibility to pancreatic cancer. Korean J Intern Med. 1997;12:128–36.
28. David SS, O'Shea VL, Kundu S. Base-excision repair of oxidative DNA damage. Nature. 2007;447:941–50.
29. Klaunig JE, Kamendulis LM. The role of oxidative stress in carcinogenesis. Annu Rev Pharmacol Toxicol. 2004;44:239–67.
30. Hung RJ, Hall J, Brennan P, Boffetta P. Genetic polymorphisms in the base excision repair pathway and cancer risk: a HuGE review. Am J Epidemiol. 2005;162:925–42.
31. Duell EJ, Holly EA, Bracci PM, Wiencke JK, Kelsey KT. A population-based study of Arg399Gln polymorphism in X-Ray Repair Cross-Complementing Group1 (XRCC1) and risk of pancreatic adenocarcinoma. Cancer Res. 2002;62:4630–6.
32. Li D, Li Y, Jiao L, Chang DZ, Beinart G, Wolff RA, et al. Effects of base excision repair gene polymorphisms on pancreatic cancer survival. Int J Cancer. 2007;120:1748–54.
33. Jiao L, Hassan MM, Bondy ML, Wolff RA, Evans DB, Abbruzzese JL, et al. XRCC2 and XRCC3 gene polymorphisms and risk of pancreatic cancer. Am J Gastroenterol. 2008;103:360–7.
34. Li D, Frazier M, Evans DB, Hess KR, Crane CH, Jiao L, et al. Single nucleotide polymorphisms of RecQ1, RAD54L, and ATM genes are associated with reduced survival of pancreatic cancer. J Clin Oncol. 2006;24:1720–8.
35. Jiao L, Hassan MM, Bondy ML, Abbruzzese JL, Evans DB, Li D. The XPD Asp312Asn and Lys751Gln polymorphisms, corresponding haplotype, and pancreatic cancer risk. Cancer Lett. 2007;245:61–8.
36. Kim YI. Folate and carcinogenesis: evidence, mechanisms, and implications. J Nutr Biochem. 1999;10:66–88.
37. Larsson SC, Håkansson N, Giovannucci E, Wolk A. Folate intake and pancreatic cancer incidence: a prospective study of Swedish women and men. J Natl Cancer Inst. 2006;98:407–13.
38. Larsson SC, Giovannucci E, Wolk A. Folate intake, MTHFR polymorphisms, and risk of esophageal, gastric, and pancreatic cancer: a meta-analysis. Gastroenterology. 2006;131:1271–83.
39. Lucock M, Yates Z. Folic acid—vitamin and panacea or genetic time bomb? Nat Rev Genet. 2005;6:235–40.
40. Wang L, Miao X, Tan W, Lu X, Zhao P, Zhao X, et al. Genetic

polymorphisms in methylenetetrahydrofolate reductase and thymidylate synthase and risk of pancreatic cancer. Clin Gastroenterol Hepatol. 2005;3:743–51.
41. Matsubayashi H, Skinner HG, Iacobuzio-Donahue C, Abe T, Sato N, Riall TS, et al. Pancreaticobiliary cancer with deficient methylenetetrahydrofolate reductase genotypes. Clin Gastroenterol Hepatol. 2005;3:752–60.
42. Suzuki T, Matsuo K, Sawaki A, Mizuno N, Hiraki A, Kawase T, et al. Alcohol drinking and one-carbon metabolism-related gene polymporphisms on pancreatic cancer risk. Cancer Epidemiol Biomarkers Prev. 2008;17:2742–7.
43. Ohnami S, Sato Y, Yoshimura K, Ohnami S, Sakamoto H, Aoki K, et al. His595Tyr polymorphisms in the methionine synthase reductase (MTRR) gene is associated with pancreatic cancer risk. Gastroenterology. 2008;135:477–88.
44. Silverman DT, Brown LM, Hoover RN, Schiffman M, Lillemoe KD, Schoenberg JB, et al. Alcohol and pancreatic cancer in black and whites in the United States. Cancer Res. 1995;55:4899–905.
45. Seitz HK, Stickel F. Molecular mechanisms of alcohol-mediated carcinogenesis. Nat Rev Cancer. 2007;7:599–612.
46. Kanda J, Matsuo K, Suzuki T, Kawase T, Hiraki A, Watanabe M, et al. Impact of alcohol consumption with polymorphisms in alcohol-metabolizing enzymes on pancreatic cancer risk in Japanese. Cancer Sci. 2008;100:296–302.
47. Holick MF. Vitamin D deficiency. N Engl J Med. 2007;357:266–81.
48. Raimondi S, Johansson H, Maisonneuve P, Gandini S. Review and meta-analysis on vitamin D receptor polymorphisms and cancer risk. Carcinogenesis. 2009;30:1170–80.
49. Campbell FC, Xu H, El-Tanani M, Crowe P, Bingham V. The Yin and Yang of vitamin D receptor (VDR) signaling in neoplastic progression: operational networks and tissue-specific growth control. Biochem Pharmacol. 2010;79:1–9.
50. Stolzenberg-Solomon RZ. Vitamin D and pancreatic cancer. Ann Epidemiol. 2009;19:89–95.
51. Garland CF, Gorham ED, Mohr SB, Garland FC. Vitamin D for cancer prevention: globe perspective. Ann Epidemiol. 2009;19:468–83.
52. Filipski E, King VM, Li X, Granda TG, Mormont MC, Liu X, et al. Host circadian clock as a control point in tumor progression. J Natl Cancer Inst. 2002;94:690–7.
53. Davis S, Mirick DK. Circadian disruption, shift work and risk of cancer: a summary of the evidence and studies in Seattle. Cancer Causes Control. 2006;17:539–45.
54. IARC. IARC monographs on the evaluation of carcinogenic risks to humans; volume 98, Shift work, painting and fire-fighting. Lyon: International Agency for Research on Cancer.
55. Brzezinski A. Melatonin in humans. N Engl J Med. 1997;336:186–95.
56. Bouatia-Naji N, Bonnefond A, Cavalcanti-Proença C, Sparsø T, Holmkvist J, Marchand M, et al. A variant near MTNR1B is associated with increased fasting plasma glucose levels and type 2 diabetes risk. Nat Genet. 2009;41:89–94.
57. Lyssenko V, Nagorny CL, Erdos MR, Wierup N, Jonsson A, Spégel P, et al. Common variant in MTNR1B associated with increased risk of type 2 diabetes and impaired early insulin secretion. Nat Genet. 2009;41:82–8.
58. Prokopenko I, Langenberg C, Florez JC, Saxena R, Soranzo N, Thorleifsson G, et al. Variants in MTNR1B influence fasting glucose levels. Nat Genet. 2009;41:77–81.
59. Mühlbauer E, Peschke E. Evidence for the expression of both the MT-1 and in addition, the MT-2-melatonin receptor, in the rat pancreas, islet and beta-cell. J Pineal Res. 2007;42:105–6.
60. Fu L, Lee CC. The circadian clock: pacemaker and tumour suppressor. Nat Rev Cancer. 2003;3:350–61.
61. Zhu Y, Stevens RG, Hoffman AE, Fitzgerald LM, Kwon EM, Ostrander EA, et al. Testing the circadian gene hypothesis in prostate cancer: a population-based case–control study. Cancer Res. 2009;69:9315–22.
62. McCarty MF. Insulin secretion as a determinant of pancreatic cancer risk. Med Hypotheses. 2001;57:146–50.
63. Saltiel AR, Kahn CR. Insulin signaling and the regulation of glucose and lipid metabolism. Nature. 2001;414:799–806.
64. Bergmann U, Funatomi H, Yokoyama M, Beger HG, Korc M. Insulin-like growth factor I overexpression in human pancreatic cancer: evidence for autocrine and paracrine roles. Cancer Res. 1995;55:2007–11.
65. Lin Y, Tamakoshi A, Kikuchi S, Yagyu K, Obata Y, Ishibashi T, et al. Serum insulin-like growth factor-I, insulin-like growth factor binding protein-3, and the risk of pancreatic cancer death. Int J Cancer. 2004;110:584–8.
66. Wolpin BM, Michaud DS, Giovannucci EL, Schernhammer ES, Stampfer MJ, Manson JE, et al. Circulating insulin-like growth factors axis and the risk of pancreatic cancer in four prospective studies. Br J Cancer. 2007;97:98–104.
67. Suzuki H, Li Y, Dong X, Hassan MM, Abbruzzese JL, Li D. Effect of insulin-like growth factor gene polymorphisms alone or in interaction with diabetes on the risk of pancreatic cancer. Cancer Epidemiol Biomarkers Prev. 2008;17:3467–73.
68. Blobe GC, Schiemann WP, Lodish HF. Role of transforming growth factor β in human disease. N Engl J Med. 2000;342:1350–8.
69. Massagué J. TGFβ in cancer. Cell. 2008;134:215–30.
70. Truty MJ, Urrutia R. Basics of TGF-β and pancreatic cancer. Pancreatology. 2007;7:423–35.
71. Tascilar M, Skinner HG, Rosty C, Sohn T, Wilentz RE, Offerhaus GJ, et al. The SMAD4 protein and prognosis of pancreatic ductal adenocarcinoma. Clin Cancer Res. 2001;7:4115–21.
72. Kaklamani VG, Hou N, Bian Y, Reich J, Offit K, Michel LS, et al. TGFBR1*6A and cancer risk: a meta-analysis of seven case–control studies. J Clin Oncol. 2003;21:3236–43.
73. Williams CS, Mann M, DuBois RN. The role of cyclooxygenase in inflammation, cancer, and development. Oncogene. 1999;18:7908–16.
74. Juuti A, Louhimo J, Nordling S, Ristimäki A, Haglund C. Cyclooxygenase-2 expression correlates with poor prognosis in pancreatic cancer. J Clin Pathol. 2006;59:382–6.
75. Zhao D, Xu D, Zhang X, Wang L, Tan W, Guo Y, et al. Interaction of cyclooxygenase-2 variants and smoking in pancreatic cancer: a possible role of nucleophosmin. Gastroenterology. 2009;136:1659–68.
76. Duell EJ, Casella DP, Burk RD, Kelsey KT, Holly EA. Inflammation, genetic polymorphisms in proinflammatory genes TNF-A, RANTES, and CCR5, and risk of pancreatic

adenocarcinoma. Cancer Epidemiol Biomarkers Prev. 2006;15:726–31.
77. Risch HA. Etiology of pancreatic cancer, with a hypothesis concerning the role of N-nitroso compounds and excess gastric acidity. J Natl Cancer Inst. 2003;95:948–60.
78. Hardy J, Singleton A. Genome-wide association studies in human disease. N Engl J Med. 2009;360:1759–68.
79. Jones S, Zhang X, Parsons DW, Lin JC, Leary RJ, Angenendt P, et al. Core signaling pathways in human pancreatic cancers revealed by global genomic analysis. Science. 2008;321:1801–6.
80. Wallace DC. A mitochondrial paradigm of metabolic and degenerative diseases, aging, and cancer: a dawn for evolutionary medicine. Annu Rev Genet. 2005;39:359–407.
81. Navaglia F, Basso D, Fogar P, Sperti C, Greco E, Zambon CF, et al. Mitochondrial DNA D-loop in pancreatic cancer: somatic mutations are epiphenomena while the germline 16519 T variant worsens metabolism and outcome. Am J Clin Pathol. 2006;126:593–601.
82. Halfdanarson TR, Wang L, Bamlet WR, de Andrade M, McWilliams RR, Cunningham JM, et al. Mitochondrial genetic polymorphisms do not predict survival in patients with pancreatic cancer. Cancer Epidemiol Biomarkers Prev. 2008;17:2512–3.
83. Wang L, Bamlet WR, de Andrade M, Boardman LA, Cunningham JM, Thibodeau SN, et al. Mitochondrial genetic polymorphisms and pancreatic cancer. Cancer Epidemiol Biomarkers Prev. 2007;16:1455–9.
84. Wain LV, Armour JA, Tobin MD. Genomic copy number variation, human health, and disease. Lancet. 2009;374:340–50.
85. Krechler T, Jachymova M, Pavlikova M, Vecka M, Zeman M, Krska Z, et al. Polymorphism -23HPhI in the promoter of insulin gene and pancreatic cancer: a pilot study. Neoplasma. 2009;56:26–32.
86. Lucito R, Suresh S, Walter K, Pandey A, Lakshmi B, Krasnitz A, et al. Copy-number variants in patients with a strong family history of pancreatic cancer. Cancer Biol Ther. 2007;10:1592–9.

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

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Supported by Grant-in-Aid from the Third Term Comprehensive Control Research for Cancer, the Ministry of Health, Labour and Welfare, Japan
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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

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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. VII, 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

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