G. 研究発表

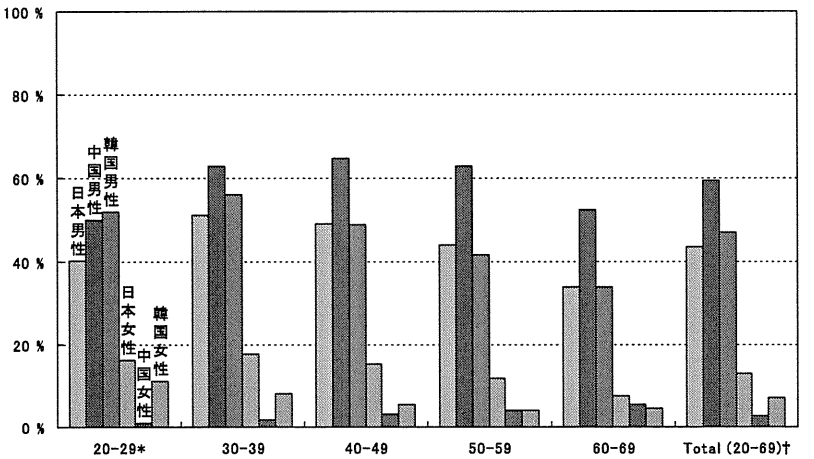
論文発表

なし

H. 知的財産権の出願・登録状況

なし

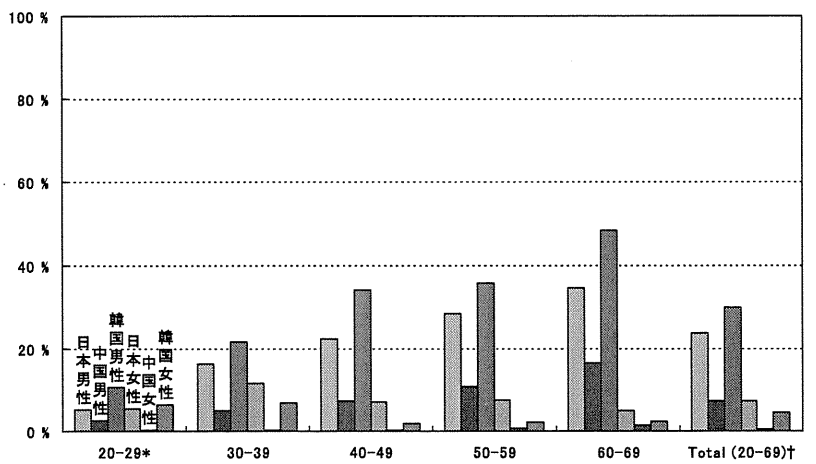
MPOWER Monitoring
Adult prevalence of current smoking



* 18-29 years old for China, 19-29 years old for South Korea; † 18-69 years old for China; 19-69 years old for South Korea.

日本: 国民健康・栄養調査(2009); >=100 cigarettes in the lifetime & [currently daily or sometimes smoking
中国: 中国慢性病及其危険因素計測分析報告(2007) ; >=100 cigarettes in the lifetime & currently smoking
韓国: Korean National Health & Nutrition Examination Survey (2009); >=100 cigarettes in the lifetime & currently smoking

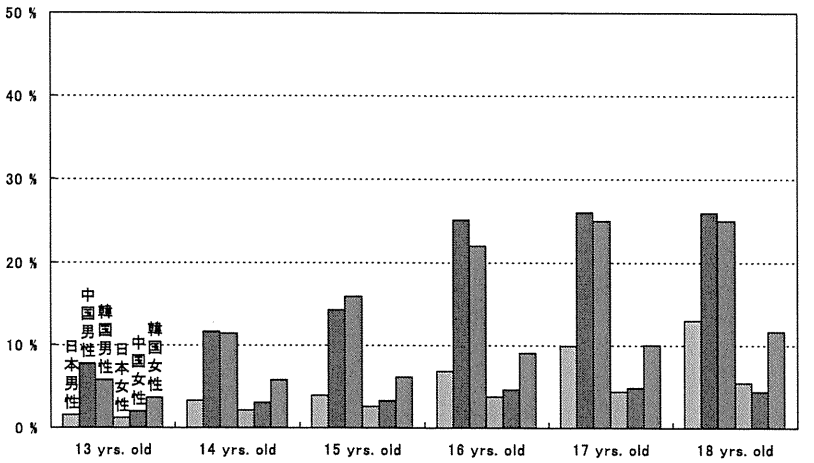
MPOWER Monitoring
Adult prevalence of former smoking



* 18-29 years old for China, 19-29 years old for South Korea; † 18-69 years old for China; 19-69 years old for South Korea.

日本: 国民健康・栄養調査(2009); >=100 cigarettes in the lifetime & currently non-smoking
中国: 中国慢性病及其危険因素計測分析報告(2007) ; >=100 cigarettes in the lifetime & currently non-smoking
韓国: Korean National Health & Nutrition Examination Survey (2009); >=100 cigarettes in the lifetime & currently non-smoking

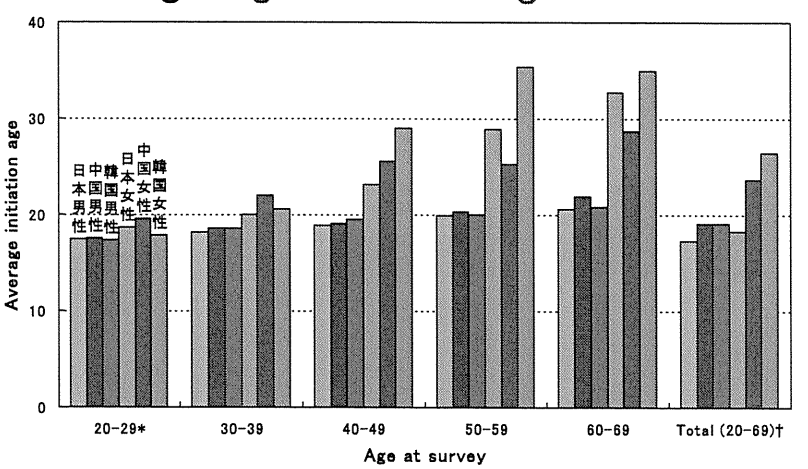
MPOWER Monitoring
Youth prevalence of monthly smoking



§ The ages correspond to the grades in school, from 1st year of junior high school to 3rd year of high school.

日本: 未成年者の喫煙・飲酒状況に関する全国実態調査(2008); Smoking >= 1 day during past month
中国: 中国青少年健康相/危険行為調査総合報告(2005); Smoking during past month (exc. 1-day smokers, currently non-smokers)
韓国: Youth Health Risk Behavior Web-based Survey (2009); Having smoked 1 day or more during past month

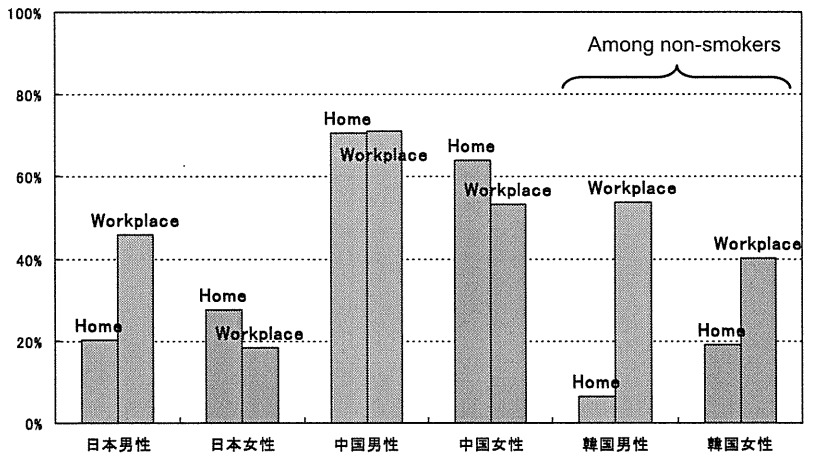
MPOWER Monitoring
Average age at smoking initiation



* 18-29 years old for China, 19-29 years old for South Korea; † 18-69 years old for China; 19-69 years old for South Korea.

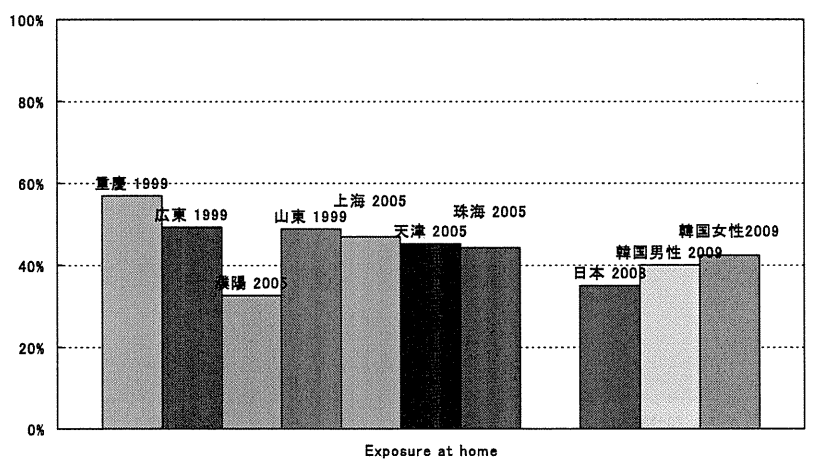
日本: 国民健康・栄養調査(2003)
中国: 中国慢性病及其危険因素計測分析報告(2007)
韓国: Korean National Health & Nutrition Examination Survey (2009)

MPOWER Protect
Passive smoking among adults



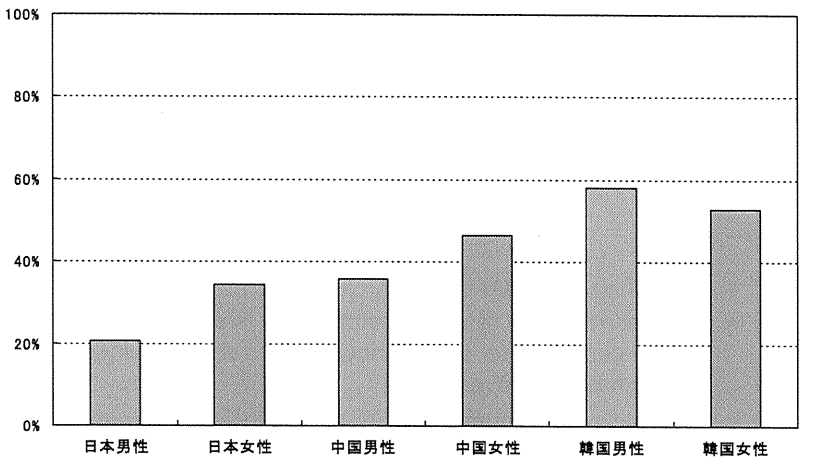
日本: National Health and Nutrition Survey in Japan (2010 data); Adults reporting exposure to tobacco smoke at home during the past month / Adults reporting exposure to tobacco smoke at work during the past month
中国: Global Adult Tobacco Survey (2010); Adults reporting tobacco smoking at home occurs at least monthly / Workers outside home who noticed tobacco smoke at workplace during the past month
韓国: Korean National Health & Nutrition Examination Survey (2009); Adults reporting exposure to tobacco smoke at home during the past month / Adults reporting exposure to tobacco smoke at indoor workplaces

MPOWER Protect
Passive smoking among youth



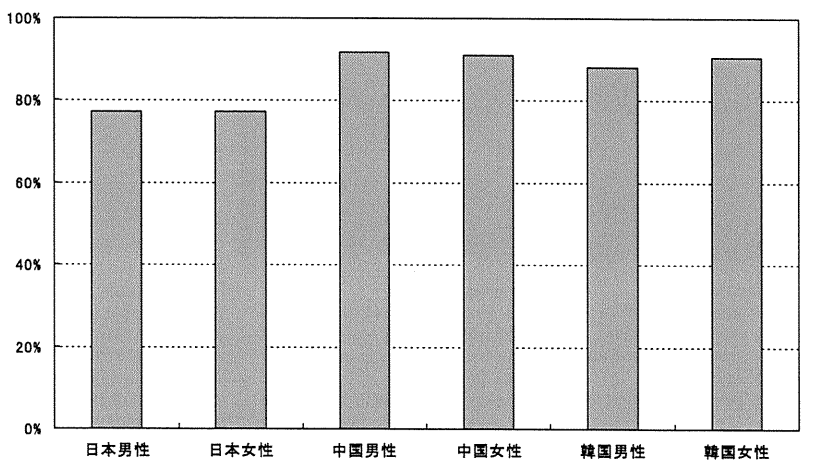
日本: 国民健康・栄養調査(2008); >= 1 day / week, among those aged 15-19 yrs.
中国: Tobacco Control15(Supple II),ii4-19,2006 (Global Youth Tobacco Survey); Someone's smoking in the presence of participants >= 1 day during past week, among those aged 13-15 yrs.
韓国: Youth Health Risk Behavior Web-based Survey (2009); Exposed 1 day/week or more, among those aged 14-19 yrs.

MPOWER Offer
Quit attempt rate



日本: Nationwide Survey on Adult Smoking Behavior and Passive Smoking Exposure (2010); Tried to quit during the past year
中国: Global Adult Tobacco Survey (2010); Tried to quit during the past year
韓国: National Smoking Prevalence Survey (2010) ; Made a quit attempt for 1 day or longer during the past year

MPOWER Offer
Quit attempt without assistance



日本: Nationwide Survey on Adult Smoking Behavior and Passive Smoking Exposure (2010); Smokers who used pharmacotherapy, counseling/advise, or other cessation methods among those who made a quit attempt during the past year中国: Global Adult Tobacco Survey (2010); Smokers who used pharmacotherapy, counseling/advise, or other cessation methods among those who made a quit attempt during the past year
韓国: National Smoking Prevalence Survey (2010) ; Smokers who made a quit attempt with no assistance (by him/herself) among those who made a quit attempt during the past year

MPOWER Offer
Evidence-based cessation support drugs

Japan
- OTC: Nicotine gum & patch
- Rx: Nicotine patch & varenicline, both covered by health insurance under several conditions

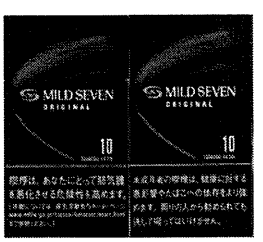
China
- OTC: Nicotine gum and patch
- Rx: 悦亭(Bupropion), 暢沛(Varenicline)

Korea
- OTC: Nicotine gum & patch
- Rx: Free nicotine replacement therapy is available in 256 public health center under the nationwide cessation services managed by the national government.
  Varenicline and bupropion are available with payment.

Japan: Guidelines for Smoking Cessation Treatment, 3rd Edition (2010)
China:「簡短戒烟干預手冊」(2007)
Korea: Guidelines for Health Promotion Program in Public Health Center (2011)

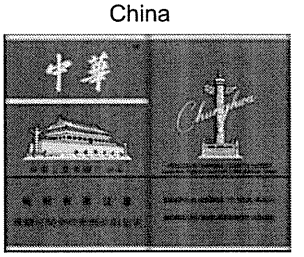
MPOWER Warn
Warning on label

Japan



Front [in Japanese]
Smoking increases the risk of worsening your emphysema. (Detailed information is available at the MHLW website www.mhlw.go.jp/topics/tobacco/main.html)
Back [in Japanese]
Smoking among minors worsens adverse health effects and tobacco dependence. You must not smoke even urged to do so by the people around you.

China



Front [in Chinese]
Smoking is harmful to your health. Quit smoking early is good for your health. [in Chinese]
Back [in English]
Smoking is harmful to your health. Smoking can cause respiratory diseases.

South Korea

Front [in Korean]
Warning: Smoking is harmful to your health. Once you start, it is very difficult to quit. Tobacco smoke includes carcinogens such as naphthylamine, nicotine, benzene, arsenic, and cadmium.
Back [in Korean]
(Same as the front label)

厚生労働科学研究費補助金(第3次対がん総合戦略研究事業)
分担研究報告書

日中間におけるがん予防対策に関連する研究連携に関する研究

研究分担者　研究分担者　林 櫻松　愛知医科大学医学部公衆衛生学 准教授

研究要旨

食道がんのリスク要因について日中間で比較を行った。日本と比較して中国では喫煙、飲酒と食道がんとの関連はそれほど強くない。世界でも有名な食道がんの好発地域として知られている中国の華北地区の太行山脈（河北省、河南省、山西省）では、家族歴や低栄養以外の発生要因はほとんど明らかにされていないのが現状である。これらの地域では胃がんに占める噴門部胃がんの割合が高いという特徴もある。文献検索、現地視察、日中双方の研究者の協議などを通じて、食道がん・噴門部胃がんのリスク要因の探索を目的とする日中共同研究を実施することで双方が合意した。食道がん好発地域である中国河北省磁県における日中共同研究の計画を作成した。DNA adductome 分析を含んだ multidisciplinary approach を取り入れた症例対照研究により、中国の食道がん好発地域での食道がんリスク要因の解明に貢献することが期待できる。

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賀宇彤 河北省腫瘤研究所 教授
喬友林 中国医学科学院腫瘤医院腫瘤研究所 流行病学研究室 主任

A. 研究目的

食道がんのリスク要因について日中間で比較を行い、食道がん好発地域である中国河北省磁県における日中共同研究の内容を具体化することを目的とする。

B. 研究方法

食道がんのリスク要因に関する日中比較を行うために、国際学術雑誌に掲載されている食道がんに関する日中両国の疫学研究、臨床研究、translational research の論文を引用した。

2011 年 8 月に河北省石家荘や磁県にて中国側の研究者と共同研究の実施にむけて詳細な討議を行った。また、2011 年 11 月に北京での日中ワークショップで中国側のがん疫学研究者との交流を通じて得た情報を分析した。

(倫理面での配慮)

既に公開されている文献をもとに考察するので、倫理面での問題はない。来年度実施予定の共同研究については、両国の倫理委員会の承認を条件にしている。

C. 研究結果

1. 食道がんリスク要因に関する日中両国の比較

1)記述疫学

Globocan によれば、日本では 2008 年 1 年間の食道がんの推計罹患数は 17,497 人、死亡数は 11,746 人であった。食道癌による死亡の男女比は約 6:1 と男性が圧倒的に多い。一方、中国では 2008 年 1 年間の食道がんの推計罹患数は 259,235 人、死亡数は 211,084 人であった。食道癌による死亡の男女比は 2:1 であった。

世界人口で調整した年齢調整罹患率(人口 10 万人あたり)を比較すると、日本は 5.7、中国は 16.7 と中国のほうが約 3 倍高かった。中国の華北地区の太行山脈（河北省、河南省、山西省）は、世界でも有名な食道がんの好発地域である。河北省の南端に位置する磁県では、2007 年の食道がん年齢調整罹患率は男性で 170（人口 10 万人あたり）、女性で 105(人口 10 万人あたり)と高かった。近年、罹患率が低下しつつあるものの、上海や北京などの大都会に比べて依然として高率で推移している。

2. リスク要因

日本では喫煙と飲酒が食道がんの最も重要なリスク要因である。今まで実施された 4 件のコホート研究と 13 件の症例対照研究の結果によると、喫煙と飲酒がすべての研究でそれぞれ食道がんリスクを上昇させた。最近のメタアナリシスでは、非飲酒者に対する飲酒者の食道がんに罹患する相対危険度は 3.30 (95%信頼区間 2.30-4.74)で、非喫煙者に対する喫煙者の食道がんに罹患する相対危険度は 3.01 (95%信頼区間 2.30-3.94)とそれぞれリスク上昇と関連している。また、食道がんにおける喫煙と飲酒との交互作用が多くの研究で観察されている。人口寄与危険度割合は男性では 84.8%女性では 51.6%と推計されている。

中国でも、喫煙と飲酒は食道がんリスクと正の関連があるとする報告が多い。最近のメタアナリシスでは非飲酒者と比較して飲酒者の食道がんに罹患するオッズ比は 1.78(95%信頼区間 1.38-2.30)と統計学的に有意な関連が認められた。しかし、好発地域に限った研究では、有意な関連が認められない、あるいは認めたとしても弱い関連しか認められなかった。喫煙に関しても同様の傾向と言える。

3) ゲノムワイド関連分析(GWAS)からの結果

2010 年以降、中国人を対象とした 3 件の GWAS が Nature Genetics に掲載され、3 件の研究で共通しているのは、食道がん感受性遺伝子座は 10q23 にある *PLCE1* であることが分かった。*PLCE1* は細胞の増殖、分化、アポトーシス、血管新生を調節する作用がある。Wu らの GWAS によれば、食道がんの発生には複数遺伝子座の多型及び遺伝・環境要因の交互作用が関与していることが分かった。

一方日本では食道がんに関する GWAS は 2 件の報告があり、いずれもアルコール代謝遺伝子がリスクと有意な関連が認められている。感受性遺伝子のリスク多型と飲酒・喫煙との両方を有する場合の食道がんリスクが 100 倍以上と著しく上昇していた。

2. 共同研究の計画について

文献検索、現地視察、日中双方の研究者の協議などを通じて、食道がん・噴門部胃がんのリスク要因の探索を目的とする日中共同研究を実施することで双方が合意した。方法としては multidisciplinary approach を取り入れた症例対照研究により遺伝要因と環境要因を検討する。症例対照研究に先立ち、2 つの先行研究を計画した。一つ目の研究は、DNA 損傷の程度を把握するために、食道がんの高率と低率地域においてそれぞれ 30 人を対象に DNA adductome 分析を実施する。DNA adductome 分析とは、DNA 付加体を網羅的に解析しカタログ化する方である。二つ目の先行研究は、磁県で行われている食道がんの早期発見スクリーニングプログラムに参

加する一般住民から 1000 人を対象にヘリコバクター・ピロリ菌の感染率や血中微量栄養素を調査する。症例対照研究では、食道がん症例 600 人、噴門部胃がん症例 200 人、一般住民対照 800 人を対象とし、遺伝要因と環境要の両方を詳細に検討する。方法としては、multidisciplinary approach を取り入れ、生活習慣に関する情報を収集するとともに、血液も採取する。さらに、2 つの先行研究から得られた有意な biomarker などについて症例対照研究で確認することも計画している。

D. 考察

中国における食道がんの罹患数は世界全罹患数の約半分を占め、がん対策上大きな負担となっている。日本や欧米と異なり、中国の好発地域では、喫煙・飲酒との関連が弱いことから、喫煙・飲酒とは別の強力なリスク要因が存在することが強く示唆された。ニトロソアミンを含んだ食事が食道がんに関連すると昔から疑われていたが、曝露の定量化やニトロサミンの由来の特定が困難なため、ニトロソアミンと食道がんリスクとの因果関係については疫学研究からのエビデンスはまだ不十分である。

2009 年以降、日中両国から食道がんの GWAS から食道がんの発生に関与する新しい遺伝子多型が報告されたが、それらの遺伝子多型の生物学的機能や飲酒などの環境要因との交互作用についてさらに検討が必要である。中国での GWAS から得られたもう一つ重要な知見は、*PLCE2* が食道扁平上皮がんと噴門部胃がんの両方に有意に関連しているということである。食道扁平上皮がんと噴門部胃がんになんらかの共通メカニズムが作用することが強く示唆された。

文献検索、現地視察、日中双方の研究者の協議などを通じて、食道がん・噴門部胃がんのリスク要因の探索を目的とする日中共同研究を実施することで双方が合意した。Multidisciplinary approach を取りいれた症例対照研究では、環境がん物質の同定、biomarker の開発、発癌リスクにかかわる DNA 損傷の総合的な評価などにおいて、より詳細な検討ができるようになる。

食道がんは早期発見が困難で、ハイリスク集団を見つけ出し予防を講じることが重要と考えられる。日本では喫煙と飲酒が食道がんの確立したリスク要因であるため、禁煙と節酒の教育が重要である。実際にアルコール依存症などハイリスク集団を対象とし、食道がんの早期発見の試みが日本で行われている。中国の好発地域では食道がんの罹患率・死亡率を低下させるために、喫煙・飲酒以外、食習慣の改善も重要と考えられる。将来は、遺伝子多型や生活習慣、発がん物質の回避などを含めた個人にあった食道がん予防が最も有効であると考えられる。

E. 結論

日中共同研究として、DNA adductome 分析を含んだ multidisciplinary approach を取り入れた症例対照研究により、中国好発地域での食道がん発生要因の解明に貢献することが期待できる。

F. 健康危険情報

なし

G. 研究発表

1. 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;17:4421-8.

2. Kikuchi S, Obata Y, Yagyu K, Lin Y, Nakajima T, Kobayashi O, Kikuichi M, Ushijima R, Kurosawa M, Ueda J. Reduced serum vascular endothelial growth factor receptor-2 (sVEGFR-2) and sVEGFR-1 levels

in gastric cancer patients. Cancer Sci. 2011;102:866-9.
3. Tamakoshi A, Lin Y, Kawado M, Yagyu K, Kikuchi S, Iso H; JACC Study Group. Effect of coffee consumption on all-cause and total cancer mortality: findings from the JACC study. Eur J Epidemiol 2011;26:285-93.
4. Tamakoshi A, Tamakoshi K, Lin Y, Mikami H, Inaba Y, Yagyu K, Kikuchi S; JACC Study Group. Number of children and all-cause mortality risk: results from the Japan Collaborative Cohort Study. Eur J Public Health 2011;21:732-7.

H. 知的財産権の出願・登録状況

なし

厚生労働科学研究費補助金(第3次対がん総合戦略研究事業)
分担研究報告書

環境発がん物質における日中間の研究連携に関する研究

研究分担者　戸塚ゆ加里　国立がん研究センター研究所 発がんシステム研究分野 ユニット長

研究要旨

中国河北省南部の磁県は食道がんの多発地域として知られている。また、この地域では噴門部胃がんの罹患数も多いことが特徴的であり、噴門部胃がんの罹患数に関してはこの20年で5倍程度増加している。これまでの調査結果から、硝酸塩の摂取、低栄養、家族歴等が食道がんの発生に関係しそうなことが報告されている。しかしながら、これらの地域における食道がん、噴門部胃がんの要因は未だに不明である。本研究では、この地域における硝酸塩の起源を調べる目的で、野菜中に存在する硝酸イオン濃度を測定し、日本産の野菜と比較してみた。地域住民に日常的に良く食べられている野菜の硝酸イオン濃度を測定した結果、ニガウリ、セロリ、白菜では、中国(磁県)産の方が高い硝酸イオン濃度を示し、キャベツでは日本産のものが高い硝酸イオン濃度を示した。このことから、同一野菜でも産地により含有する硝酸イオン濃度が異なる事がわかった。

研究協力者

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A. 研究目的

中国河北省南部の磁県は食道がんの多発地域として知られている。また、この地域では噴門部胃がんの罹患数も多いことが特徴的であり、噴門部胃がんの罹患数に関してはこの20年で5倍程度増加している。これまでの調査結果から、硝酸塩の摂取、低栄養、家族歴等が食道がんの発生に関係しそうなことが報告されている。しかしながら、これらの地域における食道がん、噴門部胃がんの要因は未だに不明である。本研究では、これら地域における硝酸塩の起源を調べる目的で、野菜中に存在する硝酸イオン濃度を測定し、日本産の野菜と比較してみた。

B. 研究方法

中国磁県で地域住民に良く食されている野菜(ピーマン、トマト、ニガウリ、じゃがいも、茄子、キャベツ、レタス、セロリ、白菜)の可食部をみじん切りにし、野菜絞り器で菜汁を採取した。菜汁中の硝酸イオン濃度は、簡便型の硝酸イオンメータ(Compact NO^{3-} meter, twinNO^{3-}, HORIBA)にて測定した。測定値は3 回測定値の平均とした。同様の方法で日本産の野菜についても硝酸イオン濃度の測定を行った。

(倫理面での配慮)

動物実験を実施する場合やヒト由来試料等を使用す

る場合には、各班員が所属する研究機関の倫理委員会の承認を得たのち行う。特に被験者の人権の擁護、個人情報の保護に十分配慮し、得られた試料は目的とする項目のみの測定に使用し、被験者の個人情報は調査以外の目的には用いないことする。組換えDNA実験を行う場合には、各班員の所属する研究機関の委員会の許可を得たのち規定に従い実施する。また、本研究では、変異原物質や発がん性が予想される化合物を扱うことから、それらによる環境汚染を起こさないよう、取扱いに十分注意して実験を行う。

C. 研究結果

野菜中の硝酸イオン濃度を測定した結果、レタス、セロリ、白菜の硝酸イオン濃度がいずれの産地においても 1000 ppm 以上の高値を示した。野菜中の硝酸イオン濃度をそれぞれの産地で比較してみたところ、ピーマン、トマト、じゃがいも、茄子、レタスでは産地による違いは見られなかった。しかし、ニガウリ、セロリ、白菜では、中国(磁県)産の方が日本産のものよりも高い硝酸イオン濃度を示し、中でもニガウリと白菜では約2倍となっていた。一方、キャベツでは日本産の方が中国(磁県)産よりも約2倍の値を示した。

D. 考察

野菜中硝酸イオン濃度を比較してみた結果、同一野菜でも産地により含有する硝酸イオン濃度が異なる事がわかった。恐らくこれは、各産地の土壌中の硝酸イオン濃度に影響されていると思われる。今回は中国食道がん多発地域(磁県)と日本との比較を行なったが、今後は同じ中国の食道がん低発地域における野菜中の硝酸イオン濃度の比較を行なう予定である。また、同様な手法を用いて、それぞれの地域における土壌中や飲料水中の硝酸イオン濃度の測定を行なうことが望ましいと考えられる。更に、これら地域住民の実際の曝露レベルを把握するために、尿中の硝酸イオン濃度についても測定し、食道がん多発地域における食道がん発症との関連性について調べる予定である。

E. 結論

野菜中硝酸イオン濃度を比較してみた結果、同一野菜でも産地により含有する硝酸イオン濃度が異なる事がわかった。

F. 健康危険情報

なし

G. 研究発表

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H. 知的財産権の出願・登録状況

研究成果の刊行に関する一覧表

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Attributable causes of cancer in Japan in 2005—systematic assessment to estimate current burden of cancer attributable to known preventable risk factors in Japan

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Background: To contribute to evidence-based policy decision making for national cancer control, we conducted a systematic assessment to estimate the current burden of cancer attributable to known preventable risk factors in Japan in 2005.

Methods: We first estimated the population attributable fractions (PAFs) of each cancer attributable to known risk factors from relative risks derived primarily from Japanese pooled analyses and large-scale cohort studies and the prevalence of exposure in the period around 1990. Using nationwide vital statistics records and incidence estimates, we then estimated the attributable cancer incidence and mortality in 2005.

Results: In 2005, ~55% of cancer among men was attributable to preventable risk factors in Japan. The corresponding figure was lower among women, but preventable risk factors still accounted for nearly 30% of cancer. In men, tobacco smoking had the highest PAF (30% for incidence and 35% for mortality, respectively) followed by infectious agents (23% and 23%). In women, in contrast, infectious agents had the highest PAF (18% and 19% for incidence and mortality, respectively) followed by tobacco smoking (6% and 8%).

Conclusions: In Japan, tobacco smoking and infections are major causes of cancer. Further control of these factors will contribute to substantial reductions in cancer incidence and mortality in Japan.

Key words: cancer, Japan, population attributable fraction, risk factor

introduction

Japan has experienced a drastic change in disease structure and pattern over the past five decades [1, 2], due to economic, demographic, and lifestyle changes experienced after World War II. Together with rapid aging, the transition in patterns of disease from communicable diseases such as tuberculosis and pneumonia to noncommunicable diseases, including cancer [1, 2], poses challenges to health systems and to public health in Japan. Cancer has been the leading cause of death in Japan since 1981, accounting for ~30% of all deaths in recent years. Cancer registry data in 2005 suggest that 54% of Japanese men and 41% of Japanese women will be diagnosed with cancer during their lifetime [3].

It is well known that cancers are largely caused as a result of lifestyle and environmental factors that are potentially preventable. On the other hand, substantial differences in the pattern of cancer by geographical region and socioeconomic level may be identified [4]. Cancer control policies in any country must therefore be tailored to reflect the local burden of cancer and characteristics of the health system.

The first national systematic quantitative assessment of multiple cancers was reported in the United States in 1981 [5] and was followed by updated estimates for the United States [6, 7], estimates for European countries including the Nordic countries [8, 9], and France [10, 11] and global estimates [12]. Although the cancer burden attributable to sectioned individual risk factors has been reported for East Asian countries [13–16], no single study has provided a reliable estimation of attributable fraction for known risk factors on multiple cancer risks in Japan.

In the present study, we conducted a systematic assessment to estimate the current burden of cancer attributable to known preventable risk factors in Japan in 2005.

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methods

We estimated the population attributable fraction (PAF) of site-specific cancers occurring in Japan in 2005. PAF in the present study is the fraction of total cancer incidences or mortality that is attributable to a particular exposure and that could be avoided if that exposure were eliminated or reduced to an alternative scenario that would result in the lowest risk, or in other words, the theoretical minimum risk exposure distribution [17].

data sources

Estimation of PAF of known causes of cancer in Japanese requires the availability of cancer incidence and mortality data in Japan, data on the prevalence of exposure to each risk factor and relative risk (RR) for each causally related cancer.

selection of risk factors for cancer in Japan. Risk factors included in this study were those for which there is evidence for a causal association with cancer (Table 1). These factors were selected based on the agents classified by the International Agency for Research on Cancer (IARC) [18] as Group 1 carcinogens in humans; risk and protective factors that were judged as 'convincing', with the exception of 'convincing' or 'probable' for vegetable, fruit, and salt intake by the second 'Food, Nutrition, Physical Activity, and the Prevention of Cancer: a Global Perspective' report, produced by the World Cancer Research Fund and American Institute for Cancer Research in 2007 [19]; and the conditions evaluated by the IARC Cancer Prevention Handbook Series [20] as causally associated with a reduced risk. Some established carcinogens, such as infection with *Schistosoma haematobium* (blood fluke), *Opisthorchis viverrini* (liver fluke), human immunodeficiency virus, and intake of aflatoxin, were not included in this study due to their very rare or very low prevalence in Japan. Further, due to the lack of reliable prevalence data in Japan, we did not include risk factors such as occupational exposure, air pollution, and ultraviolet and radiation exposure.

cancer incidence and mortality in Japan in 2005. Cancer incidence data in 2005 were obtained from the annual estimate by the Japan Cancer Surveillance Research Group as part of the Monitoring of Cancer Incidence in Japan project [3] on the basis of data collected from population-based cancer registries in Japan. We obtained sex- and age-specific incidence data for target cancers using code of the International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10), with morphology code of the International Classification of Disease for Oncology, 3rd Edition (ICD-O-3).

Data on cancer mortality statistics in 2005 were obtained from the vital statistics of Japan. We extracted sex-, age-, and cause-specific mortality from an electronic database obtained from the Japanese Ministry of Health, Labour and Welfare, with permission. Cause of death was classified using the ICD-10.

Table 2 summarizes cancer incidence and mortality in Japan in 2005.

prevalence of exposures to each risk factor. The current burden of cancer reflects the cumulative effect of past exposures. For most cancers and risk factors, average latency between first exposure and diagnosis is ~15 years [11]. We therefore assumed a latency time of ~15 years and considered exposures around 1990. We collected prevalence data of exposures to each risk factor from different sources, giving priority to representative Japanese surveys. No latency time was considered and current prevalence was applied for exogenous hormone use (hormone replacement therapy and oral contraceptive use) in women given the assumption that cancer risk decreases rapidly after the cessation of use of exogenous hormones [21]. Occupational exposures such as asbestos, etc. were not included in this analysis due to a lack of reliable prevalence data in Japan.

selection of RR for each causally related cancer. Data on RR included in this study were obtained from epidemiologic studies identified from different sources, including PubMed, *Ichushi*, and websites, in either English or Japanese. We employed priority ranking for the inclusion and selection of RRs as follows: for selection, a study should include RR and corresponding 95% confidence intervals (CIs). Among these studies, highest priority was given to meta-analyses that included pooled analyses of Japanese populations. When meta-analyses were not available, we selected the most

Table 1. Risk factors and cancers included in the present analysis

Risk factor	Definition of theoretical minimum risk exposure distribution	Target cancers associated with risk factor
Tobacco smoking (active)	Never smoking	Oral and pharynx, esophagus, stomach, colorectum, liver, pancreas, larynx, lung, cervix uteri, ovary, bladder, kidney, myeloid leukemia
Passive smoking	No exposure	Lung (nonsmokers)
Alcohol drinking	No alcohol intake	Oral and pharynx, esophagus, colorectum, liver, female breast
Overweight and obesity	Body mass index <25	Colon, pancreas, postmenopausal breast, endometrial, kidney
Physical inactivity	Average daily total physical activity level + three METs/day	Colon, breast, endometrial
Vegetable intake	Higher than the lowest intake group	Esophagus, stomach
Fruit intake	Higher than the lowest intake group	Esophagus, stomach, lung
Salt intake	Intake of ≤6 g/day	Stomach
Infection	No infection	
Helicobacter pylori		Noncardia stomach, gastric MALT lymphoma
Hepatitis C virus		Liver
Hepatitis B virus		Liver
Human papillomavirus		Oral cavity, oropharynx, anus, penis, vulva, vagina, cervix uteri
Human T-cell leukemia type I		Adult T-cell lymphoma/leukemia
Epstein–Barr virus		Nasopharynx, Burkitt lymphoma, Hodgkin lymphoma
Exogenous hormone use	No use	Female breast
Hormone replacement therapy		
Oral contraceptives		

MALT, mucosa-associated lymphoid tissue; MET, metabolic equivalents.

Table 2. Incidence[a] and mortality[b] of cancer in Japan in 2005

Site	ICD-10	Men		Women		Both sexes	
		Incidence	Mortality	Incidence	Mortality	Incidence	Mortality
Oral and pharynx	C00–C14	7417	4151	3498	1528	10 915	5679
Esophagus	C15	14 818	9465	2678	1717	17 496	11 182
Stomach	C16	80 102	32 643	37 035	17 668	117 137	50 311
Colon	C18	37 126	13 436	31 069	13 685	68 195	27 121
Rectum	C19–C20	22 344	8710	13 517	4999	35 861	13 709
Anus	C21	430	137	248	130	678	267
Liver	C22	28 729	23 203	13 465	11 065	42 194	34 268
Gall-bladder, etc.	C23–C24	9237	7845	9399	8741	18 636	16 586
Pancreas	C25	13 108	12 284	11 691	10 643	24 799	22 927
Sinonasal	C30–C31	826	261	673	174	1499	435
Larynx	C32	3903	1006	214	84	4117	1090
Lung	C33–C34	58 264	45 189	25 617	16 874	83 881	62 063
Skin	C44	4405	347	3702	321	8107	668
Breast	C50	312	87	47 582	10 721	47 894	10 808
Vulva	C51			704	226	704	226
Vagina	C52			221	102	221	102
Cervix uteri	C53			8474	2465	8474	2465
Corpus uteri	C54			8189	1459	8189	1459
Ovary	C56			8304	4467	8304	4467
Penis	C60	308	128			308	128
Prostate	C61	42 997	9265			42 997	9265
Kidney	C64	6871	2600	3153	1233	10 024	3833
Renal pelvis	C65–C66, C68	2887	1419	1731	880	4618	2299
Bladder	C67	12 619	4141	3858	1888	16 477	6029
Thyroid	C73	2126	446	7093	1024	9219	1470
Hodgkin disease	C81	422	89	501	43	923	132
Non-Hodgkin lymphoma	C82–C85, C96	8571	4772	7386	3676	15 957	8448
Multiple myeloma	C88–C90	2242	1972	2171	1917	4413	3889
Leukemia	C91–C95	5200	4311	3832	2972	9032	7283
All sites	C00–C97	379 436	196 603	267 366	129 338	646 802	325 941

[a]Japan Cancer Surveillance Research Group as part of the Monitoring of Cancer Incidence in Japan project [3].
[b]Vital statistics of Japan [1].
ICD-10, International Statistical Classification of Diseases and Related Health Problems, 10th Revision.

comprehensive studies of Japanese available. Results from cohort studies had priority over case–control studies. When RRs for Japanese populations were not available, we then substituted the data with those for other Asian populations and finally with non-Asian values from the literature.

analysis

PAF was calculated based on the RR of cancer associated with exposure to the risk factor and the prevalence of exposure to the risk factor in the total population (P) [22] using the following formula:

$$\mathrm{PAF} = \frac{P\times(\mathrm{RR}-1)}{P\times(\mathrm{RR}-1)+1}.$$

When RR or exposure data were reported in multiple exposure categories, they were combined in a dichotomous variable [10, 23].

Different methods were used for estimations related to infection. To estimate major infectious causes of cancer in Japanese such as *Helicobacter pylori*, hepatitis B virus and hepatitis C virus (HCV), we used an alternative formula [23, 24] based on the distribution of exposure in cases (Pc) since the prevalence of each infection among cases was more stable than that among control or reported populations in the literature:

$$\mathrm{PAF} = Pc\times\frac{\mathrm{RR}-1}{\mathrm{RR}}.$$

For other infectious agents, we applied the PAF values from a previous estimation [25] due to a lack of prevalence or RR data for Japanese.

For physical inactivity and salt intake, we derived the risk of cancer per unit increase in exposure and average RR for the whole population based on the average level of exposure, assuming a log-linear relationship between exposure and risk, by means of the following formula [10]:

$$\mathrm{Risk} = [\ln(\text{risk per unit})\times\text{average exposure level}];$$

$$\mathrm{PAF} = \frac{\mathrm{Risk}-1}{\mathrm{Risk}}.$$

To account for interactions among multiple risk factors, such as tobacco smoking and alcohol drinking, we used the following formula under the assumption of independent exposures and effect [26]:

$$PAF = 1-\prod_{i=1}^{n}(1-PAF_i),$$

where i refers to ith risk factor.

To account for uncertainty in the estimation of PAFs arising from RRs and the exposure prevalence of risk factors, the 95% CI of PAF was calculated using the variance of PAF based on a delta method, where P was the prevalence of exposure and β was defined as ln (RR):

$$\mathrm{Var(PAF)}=\frac{[Exp(\beta)-1]^2 \cdot Var(P)+[P.Exp(\beta)]^2 \cdot Var(\beta)}{\{P[Exp(\beta)-1]+1\}^4}$$

The variance of prevalence was considered null when the prevalence data were based on the whole population. When PAF was derived directly from the literature, as with some infectious agents, estimation of 95% CI was carried out under the assumption of no variability for the PAF.

results

Overall, ~55% of cancer (53% for incidence and 57% for mortality, respectively) among men was attributable to preventable risk factors in Japan. The corresponding figure was lower among women, but preventable factors still accounted for nearly 30% of cancer (28% and 30%; Table 3; detailed results of cancer burden by risk factor are shown in supplemental Appendix Tables A1–A8, available at *Annals of Oncology* online).

The estimated PAFs for each risk factor are summarized in Table 3. Tobacco smoking and infectious agents are the major risk factors for cancer in Japan, followed by alcohol drinking. Other risk factors such as salt intake, excess body mass index (BMI), vegetable intake and fruit intake, physical inactivity, and female exogenous hormone use accounted for a small share (<2%) of both cancer incidence and mortality. A substantial difference is seen in the pattern of cancer attributable to preventable risk factors by sex, primarily due to differences in the past cumulative exposure to tobacco smoking. In men, tobacco smoking, including both active and passive smoking, had the highest PAF (30% and 35% for incidence and mortality, respectively), followed by infectious agents (23% and 23%). Among women, in contrast, infectious agents had the highest PAF (18% and 19% for incidence and mortality, respectively), followed by tobacco smoking, including active and passive (6% and 8%).

Summary results for individual cancers are shown in Table 4. In both sexes, infections and tobacco smoking remained the major causes of site-specific cancer, i.e. oral cavity and pharynx, stomach, and liver in men and nasopharynx, liver, and cervix uteri in women due to both tobacco smoking and infection; esophagus, larynx, and urinary tract in men due to tobacco smoking; and anus in men and women due to infection. For other cancers, on the other hand, such as pancreas and leukemia; male prostate; and female colorectum, breast, corpus uteri, ovary, and urinary tract, no strong associations with the currently known preventable risk factors were seen.

discussion

This is the first study in Japan to systematically analyze the current burden of cancer attributable to multiple known preventable risk factors. Our study suggests that ~45% of cancer incidence and mortality in Japan in 2005 was potentially preventable.

The major advantage of the present study was the use of best available evidence from the Japanese population, particularly given that exposure–disease relationships can vary substantially between populations even after adjustment for potential confounders. A well-known example of this is the difference in tobacco smoking and BMI between Western and Asian populations [27, 28]. RRs of cancer incidence and mortality used in the present study were derived primarily from pooled analyses or large-scale cohort studies of Japanese, which enabled a more appropriate and realistic estimation than studies that extrapolate RRs from other populations.

Our results confirmed that tobacco smoking and infectious agents are currently the major causes of cancer in Japan.

The prevalence of current smokers among Japanese men has constantly decreased, from 53% in 1990 to 39% in 2005. The higher prevalence of ever smokers in 1990 (73%) than recently led to the large attribution of tobacco smoking in Japanese men. In women, in contrast, the prevalence of current smoking has been stable since 1990 (10%–11%) despite an increasing trend in younger age groups (aged 20–40 years: 11% in 1990 and 18% in 2005) [2]. We anticipate that the burden of cancer attributable to tobacco smoking will decrease in men but not in women in the next few decades due to the 20- to 30-year time lag between tobacco exposure and diagnosis.

Previous studies have consistently shown that the RR of tobacco smoking on cancer is lower in the Japanese as well as other East Asian populations than in Western populations [29]. There are several potential reasons for this. First, the uptake of smoking began later in the Japanese than in Western populations and the shortage of cigarettes during and shortly after World War II meant that consumption in this period at least was lower [27]. Secondly, Japanese nonsmokers have a higher incidence of cancers due to environmental tobacco smoke [30] and other indoor air pollutants [31]. Thirdly, susceptibility to tobacco smoke appears to have a genetic component; and finally, other lifestyle or environmental factors commonly found in the Japanese population appear to have a protective effect [27].

Another important finding from our study is its confirmation of the notion that infectious agents are a major cause of cancer in the East Asian region [16]. Its advanced socioeconomic status and high degree of hygiene and sanitation notwithstanding, Japan is not an exception: *H. pylori* and HCV are major infectious causes that account for a relatively large share of preventable cancers. In contrast, the contribution of infectious agents has recently been reported as <5% in Western populations [6, 9, 10]. The prevalence of these infectious agents shows a strong cohort effect, namely a huge variation by birth cohort, and has been declining rapidly among younger birth cohorts.

The majority of gastric cancer in Japan is derived from the noncardia stomach (91% in men and 94% in women in 2000) [32], and the prevalence of *H. pylori* is >80% in the birth cohort born before 1950 and 40%–50% in those born after 1950 [33, 34]. Because of this cohort effect, gastric cancer is expected to decline rapidly in a next few decades after the reduction of