諾率等を紹介する。

研究計画策定まで

2008年に組織された垣添班のメンバーに筆者らの一人が選定され，胸部CT検診の無作為化比較試験計画を策定することになったため，肺がん検診の専門家，疫学者，数理統計学者などの協力を得て計画を作成した。詳細は別稿 (8) に譲るが，概略を示すと，

1. 50-64歳の男女に対して，10年間の胸部CTが胸部X線に比べて40%の肺がん死亡減少効果があると見込み，妥当な応諾率，コンタミネーション (対照群に割付されたにもかかわらず他の医療機関などで胸部CTを受診してしまうこと) を設定すると，参加者は50000人が必要
2. 対照群では現行検診を10年間，研究群では喫煙者では低線量CT検診 (＋喀痰) を10回，非喫煙者では低線量CT検診は1, 3, 7年目の3回で残りは現行検診
3. X線とCTを比較する必要があるため対照群のX線受診率も高い必要があることから，それが見込める「ある年度の肺がん検診受診者」を対象とする
4. 検診費用は，同様の検査での健康保険収載の約90%とし，説明や事務的費用・追跡費用も含む。その結果，研究費用は15年で35億円超，年間2億円超となった
5. 同時に「CT測定による内臓脂肪と生活習慣病に関する大規模前向きコホート研究 (採血・腹部内臓脂肪のCTによる測定などとその後の各種疾患発症との関連を探るコホート研究)」を策定し，胸部CT検診のRCTで「対照群」となった人は参加することもできる，というオプションを提示する

この研究計画を金沢医科大学倫理委員会に提出し，2009年9月28日に承認された (受付番号No.91)。

パイロットスタディの計画とその目的

予算規模が大きいため「戦略研究」などでの採用を期待したが実現には至らなかった。そこで，パイロットスタディとして，地元との話し合いが進んでいた石川県と岡山県の一部の市町で先行して開始することになった。

このパイロットスタディの初年度の目的は，①研究全体の流れにおける多種の書類・ツールを作成する，②研究の実際における問題点を明らかにして計画を改善する，③対象者の何割が研究に参加するかを把握する，の3点であった。次年度以降では，④次年度以降のコンプライアンスとコンタミネーションがどの程度かを把握する，⑤精密検査結果を把握し，その適切性を評価すると共に精密検査システムの整備を行う，⑥検診受診により惹起される参加者の「不安感」の変化を検討する，などの目的も設定している。

参加自治体の選定

石川県では，2009年春に県内全市町村に対して，胸部CT検診の無作為化比較試験計画への参加希望に関するアンケートを行った。その際に希望のあった4市町村のうち「羽咋市」を第1候補として，市に対して研究計画を説明した結果，羽咋市はこの研究および内臓脂肪コホート研究に参加することになった。

検診日・場所の決定と共に，本年の肺がん検診終了直後に対象者の選定を行い (社会保険加入者は市町村で十分情報を把握していないため除外)，郵送で参加を募り，希望者に対して改めて受診の日時を通知する，などの段取りを決定し，以下のような書類・ツールの作成を行った。

必要な書類・ツールの作成

1. 説明会用に約17分間のインタビュー形式の説明ビデオを作成した。CT肺がん検診の効果は未確定であること・ランダマイズ・不利益・途中で研究中止となることもあること・などに関しても十分に説明した。
2. 説明用文書の作成を行った (図1)。「事前の郵送」「説明会での資料」の両用に使用できるような形式で，かつ「説明・同意文書」の内容を盛り込んだものにした。
3. 日時・場所等を見やすくした「研究参加勧奨チラシ」を作成した。
4. 仮参加申込書を作成した (図2)。「目的」「方法 (ランダマイズ)」「追跡調査」などの11項目を理解していること，適格性，および参加希望時間を確認できる書式とした。改訂版では事前のランダマイズが可能なように喫煙歴を追加した。
5. 研究参加同意書兼問診票を作成した。仮参加申込書の内容に加え，追跡調査用の個人情報，住民検診以外の検診受診，がん罹患などの情報を追加した。
6. 個人情報，問診票の内容，検診結果などを一元管理できるデータベースを作成した。
7. 羽咋市の封筒と羽咋市健康福祉課課長名での添え書きを用意してもらった。
8. 検診受診者の意識調査および不安度調査の目的で，「健康関連QOL尺度SF8の8項目」「HADS日本語版14項目のうち5, 7, 9, 14の4項目」「CT検診に関する知識とイメージを問う3項目 (我々が作成)」のアンケートを作成した。
9. 説明文書および説明会での説明内容の理解度調査のアンケートを作成した。
10. 説明会当日の流れを説明したチラシを作成した。
11. 当日不参加を決定した人のために不参加理由書を作成した。

実際のリクルート業務の流れ

1. 本年の肺がん検診受診者のうち，2011年4月1日現在で50-64歳の男女で国民健康保険加入者のリストを作成した。
2. その全員に対して，①市からの添え書き，②研究参加勧奨チラシ，③胸部CTによる肺がん検診の無作為化比較試験の説明書，④仮参加申込書，⑤返信用封筒，を，⑥羽咋市の封筒に入れて郵送した。

厚生労働省垣添班胸部CT検診小班（小班長：金沢医科大学教授　佐川元保）

肺がん検診研究プロジェクトの説明書

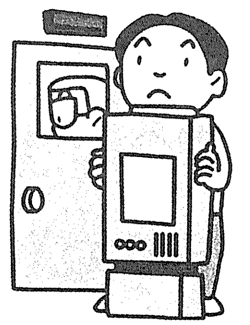
研究名：低線量CTによる肺がん検診の精度および死亡減少効果評価のための個人単位ランダム化比較試験

今なら無料で精密な検診が受けられます

なぜ、このような検診の研究が企画されたのですか？

肺がんによる死亡は増加しており、その対策は国家的にも重要です．現在日本で行われている胸部X線検査と喀痰細胞診検査は肺がんによる死亡を減らす効果があることがわかっておりますが万能ではなく、検診を受けても肺がんで亡くなる患者さんもいるのが実情です。

最近，胸部のCT検査（コンピューター断層撮影）を肺がん検診に用いる方法が一部で行われ始めました．その結果，多くの早期がんが見つかるようになったのですが，一方で，本来ならば治療する必要のないような病変も手術してしまったりする例があるのではないか，ということも危惧されており，CT検診とX線検診のどちらがより有益であるかはわかっていません．CT検診とX線検診を比べるために厚生労働省の研究班でこの研究が計画されました。全国で行う計画を立てましたが、先駆けとして全国で２つの市町が選ばれ、その一つが羽咋市です。

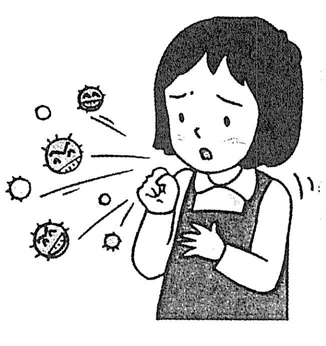


どのように行われるのですか？

CT検診は小さなものも見つかるかわり余計なものも見つけるかもしれず、X線検診より良いのかは現在のところ不明です。そのため、どちらかが「損」だの「得」だのということはありません．この研究では「CTとX線のどちらの検査法でも良い」と言っていただける方を集め，コンピューターで公平に分け、半分の方にCT、もう半分の方にX線検診を行っていただきます．

X線とCTのどちらの検査も、肺がんを数多く診断・治療している私たち専門医が、検査したフィルムを責任をもって診断します。

タバコをたくさん吸っていた方の場合は、早期がんを見つけるためには痰の検査も必要ですので、X線とCTのどちらの検査になっても、痰の検査も行います。



来年以降はどうなるのですか？

１－２年では効果が不十分ですので、この研究は10年間行う予定です。X線の方はX線を1年に1回、計10回受けることになります。一方、CTの方はタバコを吸っていたかどうかで回数が変わります。タバコを吸っていた方はCTを年に1回10年間ですが、タバコをあまり吸っていなかった方は10年間にCTを3回、X線を7回予定しています。この理由は、タバコを吸っていなかった方は3回程度で十分だろうと考えられているからです。逆にいえばタバコを吸っていた方はそれでは不十分だと考えられているのです。その点からも、なるべく早く禁煙することをお勧めします。

図1a, 1b, 1c．低線量CTによる肺がん検診の無作為化比較試験の説明書 (原本はカラー)

27

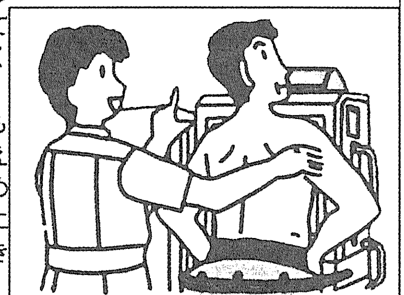
実際に参加するにはどうしたら良いのですか？

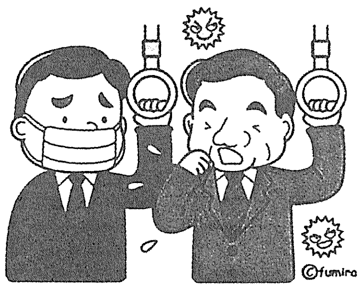
この研究に参加するには、この説明書を良く読んでいただき、内容を理解して参加しようと思われたら、同封の「参加（仮）申込書」に必要事項を書いていただき、10月に行われる3回の説明会のうち出席希望の日と午前か午後かを丸で囲んで、返信用封筒でご返送ください。

事務局であなたが参加可能であることを確認できましたら、参加決定日を記載した「参加（仮）確認書」を郵送いたします。その参加決定日に会場に来ていただいて、その場でビデオによる説明、および口頭による説明を聞いていただき、納得されたら正式に参加となります。

その後、CT検診の方とX線検診の方にわかれることになりますが、初年度は今年の分のX線検診をつい先頃受診していますので、X線をもう一度撮ることはしませんので、それで終了です。ただし、「腹部内臓脂肪CT検査＋採血検査」をオプションとして無料で受けることもできますので、御希望の方は申し出てください。CT群の方は、そのまま胸部CTを撮影していただくことになります。結果は後日お知らせします。

来年度以降も、CT群の方もX線群の方も、通常の検診よりもさらに慎重に診断しますので、通常の検診とは実施日を変えて羽咋市体育館で行う予定です。参加者の方にはあらかじめ通知いたします。その際には、通常は肺がん検診と同時に行っている特定検診なども同時に行えるように手配しておきます。





費用はかかるのですか？　何年間行うのですか？

検診で行うX線検査、CT検査、痰の検査は、いずれも事務局が負担しますので、皆さんの負担はなく、無料になります。ただし、検診で異常が見つかって医療機関で精密検査を行う場合には、通常の保険診療として通常の窓口負担が生じます。

この研究は10年間行う予定ですが、国の予算で動いているため、事業仕分けなどで予算がおりなくなれば途中で中断する可能性もあります。

CT検診で予想される利益と不利益には何がありますか？　検診で必ずがんが早期に見つかるのですか？

胸部CT検診を受けた方の予想される利益としては，肺がんによる死亡をX線よりもさらに減らすことができるかもしれない，ということが挙げられます．一方，不利益としては，第一に放射線被曝の問題が挙げられますが，今回対象の年齢の方ではそれほど問題ありません．その他の不利益としては，治療の不要な良性病変のために精密検査や手術が必要になる可能性があります．また，がんであっても非常に増大速度が遅く天寿を全うできるようなものを手術してしまう可能性もあります．あまり小さなものまで精密検査を行うと受診する方の不利益になるため、この研究では日本ＣＴ検診学会の基準に従って「要精密検査」とするように規定しています。また，CTとX線のどちらの場合でも、精密検査や治療を行っている中で医療上のトラブル・合併症に巻き込まれる可能性は0にはできませんので、そのような可能性はあります．また、非常に小さながん、急速に増大するがん、見えにくい場所にできるがんは、検診では見つけられないことがあります。

説明会および検診の日時：
平成22年　10月8日（金）
10月15日（金）
10月24日（日）
いずれも受付は9―16時
場所：羽咋市役所横体育館

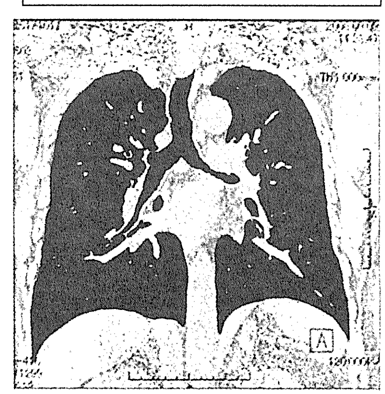


図1b.

参加するときの条件はありますか？

この研究に参加するためには、いくつかの条件があります。

1．本年の10月に3回ほど説明会を開きますので、そのいずれかの日程に出席のうえ説明を直接聞いていただき、参加の意思を確認する必要がありますので、どの日程にも出席できない人は参加できません。

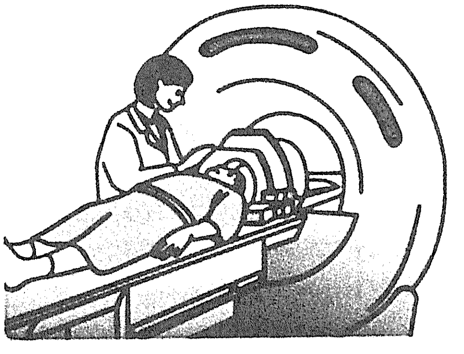
2．検診に10年間参加できそうな方（参加する意思があれば確証は不要）で、左下の「健康状態や病気に関する調査」に承諾していただける方のみ参加できます。

3．以下の方は参加できません。

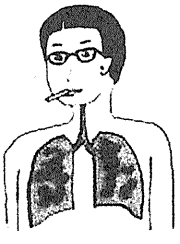
①いままで御自身が肺がんにかかったことがある人
②現在、肺がん疑いで医療機関で検査やフォローをしている人
③過去10年以内に「CTによる肺がん検診」を受診した人
④過去5年以内に、いずれかの「がん」にかかった人
⑤重篤な病気（重い心臓病、重い腎臓病など）にかかっている人

健康状態や病気に関する調査

この研究に参加される場合には、CTの方もX線の方も、後日あなたの健康状態や病気に関する調査を行わせていただく予定です。調査の方法は、ご本人あるいはご家族への手紙あるいは電話などによる問い合わせ、およびあなたが通院・入院される医療機関への調査ということになります。そのご承諾を得ることが、この研究への参加上必要ですのでご承諾をお願いします。

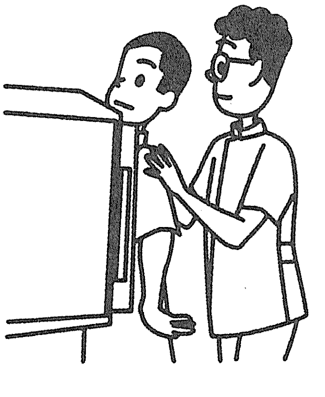


説明会および検診の日時：
平成22年　10月8日（金）
10月15日（金）
10月24日（日）
いずれも受付は9―16時
場所：羽咋市役所横体育館



腹部内臓脂肪CT検査について

最近メタボリック症候群が話題にのぼっています。X線検査の群の方は、この研究と並行して行う「採血＋腹部CTによる内臓脂肪と健康との関係を長期間観察する研究」に無料で参加することもできます。その研究では「採血」「生活習慣調査」「腹部CTによる内臓脂肪検査」を一度だけ行いますので、御希望の方は、お申し出ください。希望しない方は参加しなくて結構です。胸部CTの群の方は、予算の関係もあり両方のCTは受けられないので、その研究に参加することはできません。



参加御希望の方は、参加（仮）申込書に必要事項を記入して、参加（仮）申込書のみを返信用封筒に入れ、９月１８日必着でご返送ください。

厚生労働省垣添班　胸部CT検診小班（小班長：金沢医科大学教授　佐川元保）

事務局・問合せ先：金沢医科大学　呼吸器外科　佐川元保　電話＆FAX　076−286−1207
Email: sagawam@kanazawa-med.ac.jp

図1c.

参加（仮）申込書

（本申込書は、10月の説明会の時に書いていただきます）

研究名：低線量CTによる肺がん検診の精度および死亡減少効果評価のための個人単位ランダム化比較試験

参加するためには、説明書に載っている以下の記載に関して理解していただく必要があります。理解された場合には、右端の「理解した」の前の四角に☑を入れてください。

この研究はCT検診とX線検診とを比較するために行います	□ 理解した
研究は10年間の予定ですが継続できないこともあり得ます	□ 理解した
抽選でCTとX線に約半分ずつふりわけられます	□ 理解した
タバコを吸ってるかどうかで検査の内容がかわります	□ 理解した
CT検診では結果的に不要な検査や手術が行われる可能性があります	□ 理解した
精密検査や治療の際に合併症に巻き込まれる可能性はあります	□ 理解した
検診の費用は事務局負担、精密検査は保険診療で行われます	□ 理解した
私（参加者）の病気などの調査が行われることを承諾します	□ 理解した

事前調査（当てはまる方を丸で囲んでください。該当者は空欄を埋めてください）

現在通院中の医療機関がありますか？（ あり、なし ）

ある場合には、その医療機関名（　　　　　　　　）病名（　　　　　　　　）

現在入院中または入所中ですか？（ はい、いいえ ）

はい、の人は、その医療機関・施設名（　　　　　　　　）病名（　　　　　　　　）

過去10年間に入院したことがありますか？（ はい、いいえ ）

はい、の人は、その医療機関・施設名（　　　　　　　　）病名（　　　　　　　　）

いままで御自身が肺がんにかかったことがありますか？（ はい、いいえ ）

現在肺がん疑いで医療機関で検査やフォロー中ですか？（ はい、いいえ ）

過去10年以内に「CTによる肺がん検診」を受けましたか？（ はい、いいえ ）

過去5年以内にどこかの「がん」にかかりましたか？（ はい、いいえ ）

現在重い病気（心臓病・透析中など）にかかっていますか？（ はい、いいえ ）

私は、上記を納得して、このプロジェクトに参加しますので、この書面で申込みます。

氏名＿＿＿＿＿＿＿＿＿＿　住所＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿

第1希望（丸で囲む）10/8（金）午前、10/8（金）午後、10/15（金）午前、10/15（金）午後、10/24（日）午前、10/24（日）午後

第2希望（丸で囲む）10/8（金）午前、10/8（金）午後、10/15（金）午前、10/15（金）午後、10/24（日）午前、10/24（日）午後

第3希望（丸で囲む）10/8（金）午前、10/8（金）午後、10/15（金）午前、10/15（金）午後、10/24（日）午前、10/24（日）午後

図2. 低線量CTによる肺がん検診の無作為化比較試験の仮参加申込書

30

3．説明会参加希望者に対して，3日間で9回（午前2回，午後1回）の説明会を行った。挨拶3分，ビデオ17分，口頭での説明25分，その後，登録という流れとした。説明会当日の配布書類は，①説明会の流れを説明したチラシ，②胸部CTによる肺がん検診の無作為化比較試験の説明書（郵送したものと同じ），③その研究の同意書および問診票，④腹部内臓脂肪コホート研究の説明書（こちらの研究の同意書と問診票は，X線群に振り分けられた後で内臓脂肪コホート研究参加の意思を確認してから配布），⑤検診受診者の意識調査および不安度調査，⑥説明内容の理解度調査，である。
4．必要書類（上記3の③と⑤）への記載を終えた順に，①記載内容チェック，②登録とランダマイズ，③検査の説明，④胸部CT群は撮影票記入後に胸部CT検査，内臓脂肪コホート希望者は問診票記入・身体計測・血圧測定・採血・腹部内臓脂肪CTの順にまわる，⑤高危険群は喀痰細胞診の容器を渡される，⑥必要書類を提出し，次年度の検査予定を書いたチラシを渡され帰宅，という流れで行った。
5．説明会には参加したが，不適格あるいは意思により研究へ不参加となった場合には，上記3の⑤⑥および，別に用意した「不参加理由書」で理由を選択または記載してもらってから帰宅，という流れとした。

研究への参加応諾率

329通郵送し，117通（35.6%）の返信があった。うち1例が重篤な心疾患で，別の1例がCTによる肺がん検診の10年以内の受診歴があり不適格となった。残りの115例に対し，説明会参加日時の割り振りを行い，その通知を郵送した。その結果，数名の変更希望があったほか，1名がどの日程でも参加不能なため研究参加を断念した。残りの114名（34.7%）が説明会参加予定となった。

説明会に参加した114名中，1名が仮参加申込以降にCTによる肺がん検診を受診したため不適格，1名が10年間の研究参加に難色を示し希望せず，1名がCT検診の不利益の可能性のため希望せず，計3名が不参加となり，残りの111名（郵送した対象全体の33.7%，返信された117例中の94.9%）が研究参加となった。

考　　察

このパイロットスタディの初年度の目的は，①研究全体の流れにおける多種の書類・ツールを作成する，②研究の実際における問題点を明らかにして計画を改善する，③対象者の何割が研究に参加するかを把握する，の3点であった。

必要な書類・ツールについては，研究の準備を進めて行きながら必要に応じて多種のチラシ，説明書，添え書き，データベースファイル，問診票などを作成した。今回のパイロットスタディは小規模ではあるが，大規模に進める場合にも充分対応できる基礎的な資料を作成し得たと思われる。同様に，種々の状況で発生した問題にその場で対応し，その後の研究計画の変更に生かすことができた。

研究参加応諾率は対象の1/3に達し，この種の検診の研究への応諾率としては，大変高かった。その理由としては，第1に「本年度の肺がん検診受診者」を対象としたため，健康意識が高いのみならず肺がん検診への興味が高い集団に対してリクルートを行ったことが挙げられる。第2には羽咋市が日頃からがん検診への意識が比較的高い自治体であったため，充分な協力が得られたことが影響していた可能性がある。第3に，かつて「がん検診の無作為化比較試験は日本になじまない」と言われていた時代があったが，今や多くの住民は無作為化に関して拒否感を持たないようになったことが考えられる。最後に，胸部X線群に「内臓脂肪研究へ参加可能」という条件を付けたことが影響した可能性がある。

説明会参加者の約95%が研究参加に至った。このことは，説明会参加者のほとんどが適格症例であり，かつ説明会で詳しい説明を聞いた後も参加の意思が変化していないという点で，今回使用した勧誘の手紙は「適格症例の絞り込み」「ランダマイズなども含めた研究計画の説明」の両面において有効に機能していると見ることができると思われる。

今後，CT所見の読影・精密検査・治療・追跡，と研究を進めていく予定であるが，CT検診での初回受診者の要精査率は通常5－10%程度，肺癌発見率は1%以下と考えると，今回のパイロットスタディでは要精査以降の症例数はきわめて少数になると考えられ，パイロットスタディでできることの限界もある。一方で，今回の研究により，約1/3という高い研究参加応諾率が得られたことは，他の地区でも同様なリクルート方法を取れば，相当高い応諾率が得られることが期待される。2010年11月に米国NCIのホームページでNational Lung Screening Trialの結果概要に関する速報がなされ（http://www.cancer.gov/newscenter/pressreleases/NLSTresultsRelease：2010年11月6日アクセス），胸部CT検診による死亡減少効果を認めたとの報告がなされたが詳細は未だ不明であり，また，非喫煙者に対する効果も不明である。その点で，わが国における胸部CT検診の効果に関する評価研究を今後実行していく必要性は全く変わっておらず，充分な予算措置が講じられることが待たれる。

この研究の事務作業に御援助いただいた山本和子氏，検診実務で御援助いただいた向瀬芳野氏，和田正美氏に深謝いたします。この研究は，がん研究開発費「がん検診の評価とあり方に関する研究」班（主任研究者：垣添忠生）の胸部CT検診小班（佐川元保（小班長），祖父江友孝，西井研治，江口研二，中山富雄，林　朝茂，小林　健，佐藤俊哉，佐藤雅美，細井　牧，濱島ちさと，斎藤　博，鈴木隆一郎，三澤　潤，柿沼龍太郎，田中　良）で研究計画を作成し，同研究班の活動の一部として実施された。

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Recruitment for "A pilot study of randomized controlled trial to evaluate the efficacy of lung cancer screening by thoracic CT"

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Objective: To evaluate the efficacy of lung cancer screening by thoracic computed tomography (CT), a randomized controlled trial was planned in Japan. The randomized trial was designed as follows: 1) participants were randomly assigned into 2 groups, CT group and XP group; 2) XP group would receive 10 times of lung cancer screening by chest x-ray annually for 10 years; 3) smokers in CT group would receive 10 times of lung cancer screening by thoracic CT annually for 10 years; 4) non-smokers in CT group would receive 3 times of lung cancer screening by thoracic CT and 7 times of chest x-ray during 10 years. A pilot study was performed to evaluate the feasibility of the trial.

Methods: A letter for recruitment to participate in the above trial was mailed to the citizens in Hakui City, who were 50-64 years old and underwent regular lung cancer screening using chest x-ray this year. In the letter we explained that 1) the efficacy of lung cancer screening by thoracic CT had not been proved yet; 2) only half of the participants could undergo thoracic CT screening; 3) thoracic CT screening might cause unfavorable consequences like radiation exposure, false-positives or overdiagnosis.

Results: Of 329 persons who received the letter of recruitment, 117 replied. After meeting with us for detailed explanation, 111 persons participated in the above randomized trial.

Conclusion: The compliance of recruitment is high (approximately one third) and the above trial may be feasible.

Key Words: lung cancer screening, early detection, efficacy, thoracic CT screening

32

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SHORT COMMUNICATION

Relation between cigarette smoking and ventilatory threshold in the Japanese

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Abstract The link between cigarette smoking and ventilatory threshold (VT) was investigated. We used data for 407 men and 418 women not taking medication. Habits of cigarette smoking were obtained through interviews by well-trained staff. The influence of cigarette smoking on oxygen uptake, work rate, and heart rate at VT was evaluated. Oxygen uptake at VT in women and work rate at VT in men with cigarette smoking were significantly lower than in subjects without cigarette smoking after adjusting for age. The differences of parameters at VT did not reach significant levels after adjusting for age and exercise habits in both sexes. However, in women without exercise habits, there was significant difference of oxygen uptake at VT between women with and without cigarette smoking after adjusting for age [cigarette smoking (+): 11.5 ± 1.8 ml/kg/min, cigarette smoking (−): 12.4 ± 2.1 ml/kg/min, $p = 0.0006$]. The number of cigarettes smoked per day and the Brinkman Index were not clearly correlated with oxygen uptake at VT. A combination of promoting exercise habits and prohibiting cigarette smoking might be recommended for improving the aerobic exercise level, especially in women.

Keywords Cigarette smoking · Ventilatory threshold · Oxygen uptake · Exercise habits

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Introduction

Cigarette smoking has become an important public health challenge, and it has been reported that 39.4% of men and 11.0% of women are current smokers in Japan [1]. Cigarette smoking is also a strong risk factor for atherosclerosis and cardiovascular disease in a dose-dependent manner [2].

Exercise is considered as a useful method for preventing and improving atherosclerosis and cardiovascular disease. The ventilatory threshold (VT) is defined as the upper limit of aerobic exercise and is thought to serve as an accurate and reliable standard for exercise prescription [3]. Since the exercise intensity at VT is not harmful to cardiovascular function, it can be safely applied to patients with myocardial infarction as an exercise prescription [4]. We have previously reported that aerobic exercise level was significantly lower in subjects with metabolic syndrome than that in subjects without the syndrome [5], and the prevalence of metabolic syndrome was significantly higher in subjects with cigarette smoking than that in subjects without cigarette smoking [6]. However, the relationship between cigarette smoking and aerobic exercise level defined by VT is not fully discussed.

The aim of this study is to explore the link between cigarette smoking and VT in the Japanese population.

Subjects and methods

Subjects

We used data for 407 Japanese men (aged 42.1 ± 11.4 years) and 418 women (aged 44.8 ± 12.0 years) (5.8%), retrospectively from a database of 14,345 subjects who met the following criteria: they had (1) wanted to change their lifestyle, i.e., diet and exercise habits, and had received an annual health checkup from June 1997 to May 2007 at Okayama Southern Institute of Health, (2) they had received anthropometric and oxygen uptake at VT measurements and evaluation of cigarette smoking as part of the annual health checkup, (3) received no medications for diabetes, hypertension, and/or dyslipidemia, and (4) provided written informed consent (Table 1).

Ethical approval for the study was obtained from the Ethical Committee of Okayama Health Foundation.

Anthropometric measurements

Anthropometric and body compositions were evaluated based on the following parameters: height, body weight, abdominal circumference, and hip circumference. Abdominal circumference was measured at the umbilical level, and the hip was measured at the widest circumference over the trochanter in standing subjects after normal exhalation [7].

Cigarette smoking

The data on cigarette smoking were obtained at interviews by well-trained staff in a structured way. The subjects were asked if they currently smoked cigarettes. When the answer was "yes," they were classified as current smokers and further questions were asked regarding the average number of cigarettes smoked per day and their age at starting smoking. When the answer was "no," they were classified as nonsmokers.

Based on answers to those questions, the cumulative amount of cigarette consumption expressed as the Brinkman Index (BI: number of cigarettes consumed per day multiplied by years of smoking) [8].

Table 1 Clinical profiles of enrolled subjects

	Mean ± SD	
	Men	Women
Number of subjects	407	418
Age (years)	42.1 ± 11.4	44.8 ± 12.0
Height (cm)	169.9 ± 5.8	156.0 ± 5.5
Body weight (kg)	79.1 ± 13.3	65.0 ± 12.9
Abdominal circumference (cm)	91.1 ± 10.9	81.4 ± 11.2
Hip circumference (cm)	98.6 ± 6.8	96.7 ± 8.5
Oxygen uptake at ventilatory threshold (ml/kg/min)	14.9 ± 3.9	12.6 ± 2.5
Work rate at ventilatory threshold (W)	82.9 ± 24.4	51.3 ± 14.6
Heart rate at ventilatory threshold (beats/min)	106.0 ± 11.9	107.0 ± 11.8

Exercise testing

A graded ergometer exercise protocol [9] was performed. Two hours after breakfast, a resting electrocardiogram (ECG) was recorded and blood pressure was measured. Then, all participants were given graded exercise after 3 min of pedaling on a bicycle ergometer at zero load (Excalibur V2.0; Lode BV, Groningen, The Netherlands). The profile of incremental workloads was automatically defined using the methods of Jones et al. [9], in which the workloads reach the predicted $\dot{V}O_{2\,max}$ in 10 min. A pedaling cycle rate of 60 rpm was maintained. Loading was terminated when the appearance of symptoms forced the subject to stop. During the test, ECG was monitored continuously together with recording of heart rate (HR). Exhaled gas was collected, and rates of oxygen consumption $\dot{V}O_2$ and carbon dioxide production ($\dot{V}CO_2$) were measured breath by breath using a cardiopulmonary gas exchange system (Oxycon Alpha; Mijnhrdt b.v., The Netherlands). VT was determined by the standard of Wasserman et al. [3], Davis et al. [10], and the V-slope method of Beaver [11] from $\dot{V}O_2$, $\dot{V}CO_2$, and minute ventilation ($\dot{V}E$). At VT, $\dot{V}CO_2$ (ml/kg/min), work rate (W), and heart rate (beats/min) were measured and recorded.

Exercise habits

The data on exercise habits were obtained through interviews by well-trained staff in a structured way according to the National Nutrition Survey in Japan [12]. The subjects were asked if they currently exercise (over the level of 30 min per session, two times per week, and prolonged duration for 3 months). When the answer was "yes," they were classified as subjects with exercise habits. When the answer was "no," they were classified as subjects without exercise habits.

Statistical analysis

All data are expressed as mean ± standard deviation (SD). Statistical analysis was performed using an unpaired t test, χ^2 test, logistic regression analysis, covariance analysis, smoking were noted after adjusting for age and exercise habits in both sexes (Table 2). We separately compared oxygen uptake at VT in subjects without exercise habits. After adjusting for age, no significant difference of oxygen uptake at VT was noted between men with and without cigarette smoking [cigarette smoking (+): 13.8 ± 2.6 ml/kg/min, cigarette smoking (−): 13.8 ± 2.5 ml/kg/min, $p = 0.4089$]. However, there was significant difference of oxygen uptake at VT between women with and without cigarette smoking [cigarette smoking (+): 11.5 ± 1.8 ml/kg/min, cigarette smoking (−): 12.4 ± 2.1 ml/kg/min, $p = 0.0006$].

In addition, we compared the parameters of VT among subjects with and without cigarette smoking and exercise habits [A: cigarette smoking (+) exercise habits (+), B: cigarette smoking (−) exercise habits (+), C: cigarette smoking (+) exercise habits (−), D: cigarette smoking (−) exercise habits (−)] (Table 4). In men, oxygen uptake at VT in group C and D was significantly lower than that in group A and B. Work rate at VT in group C and D was significantly lower than that in group B. No significant differences of heart rate were not noted among the four groups. In women, oxygen uptake at VT in group C was significantly lower than that in group A and B. Work rate at VT in group A was significantly higher than that in group B, C, and D. Heart rate at VT in group D was significantly higher than that in group B. Oxygen uptake at VT in group A and B (with exercise habits) was higher than that in group C and D (without exercise habits) in both sexes, as in our previous report [5].

Finally, we evaluated the relationship between the number of cigarettes smoked per day and oxygen uptake at VT, and also between the BI and oxygen uptake at VT (Fig. 1). The number of cigarettes smoked per day was not correlated with oxygen uptake at VT in either sex (men $r = -0.172$, $p = 0.0265$; women $r = -0.294$, $p = 0.0470$). BI was also not clearly correlated with oxygen uptake at VT (men $r = -0.192$, $p = 0.0132$; women $r = -0.214$, $p = 0.1535$). In subjects without exercise habits, the number of cigarettes smoked per day was not correlated with oxygen uptake at VT in either sex (men $r = -0.072, p = 0.4487$; women $r = -0.180, p = 0.2791$). BI was also not clearly correlated with oxygen uptake at VT (men $r = -0.135$, $p = 0.1515$; women $r = -0.088$, $p = 0.5976$).

Discussion

Impairment of pulmonary oxygen exchange [13, 14], downregulation of adrenergic receptors [15], and long-term cardiac damage caused by stimulation of catecholamine by smoking [16] may also in part explain lower oxygen uptake at VT in subjects with cigarette smoking. Some cross-sectional studies show that cigarette smoking is correlated with cardiovascular fitness [17–19]. Hirsch et al. [17] evaluated the immediate effects of cigarette smoking on aerobic exercise capacity, and cigarette smoking resulted in a significantly lower $\dot{V}O_{2\,max}$ and higher heart rate after 3 cigarettes/h for 5 h. Marti et al. [18] reported that, among army conscripts, the distance covered in a 12-min endurance run was inversely related to daily cigarette consumption and years of smoking. Rotstein et al. [19] also reported that smoking retards physiological responses to submaximal exercise immediately after smoking three cigarettes. In a longitudinal analysis, Sandvik et al. [20] showed that decline in physical fitness and lung function was greater among smokers than that among nonsmokers

Table 4 Comparison of parameters at ventilatory threshold among subjects with and without cigarette smoking and exercise habits

	A Cigarette smoking (+) Exercise habits (+)	B Cigarette smoking (−) Exercise habits (+)	C Cigarette smoking (+) Exercise habits (−)	D Cigarette smoking (−) Exercise habits (−)
Men				
Number of subjects	52	112	114	129
Oxygen uptake at ventilatory threshold (ml/kg/min)	15.6 ± 3.7	16.9 ± 5.4	13.8 ± 2.6[ab]	13.8 ± 2.5[ab]
Work rate at ventilatory threshold (W)	84.8 ± 25.2	92.5 ± 31.8	77.5 ± 18.0[b]	78.6 ± 18.8[b]
Heart rate at ventilatory threshold (beats/min)	103.8 ± 12.2	104.7 ± 13.3	106.2 ± 10.3	107.7 ± 11.6
Women				
Number of subjects	8	97	38	275
Oxygen uptake at ventilatory threshold (ml/kg/min)	14.4 ± 5.0	13.2 ± 3.3	11.5 ± 1.8[ab]	12.4 ± 2.1
Work rate at ventilatory threshold (W)	70.0 ± 27.0	53.2 ± 17.3[a]	49.3±13.5[a]	50.3 ± 12.8[a]
Heart rate at ventilatory threshold (beats/min)	105.6 ± 13.3	104.1 ± 12.0	106.3±11.2	108.2 ± 11.7[b]

Mean ± SD

[a] $p < 0.05$ versus cigarette smoking (+), exercise habits (+)

[b] $p < 0.05$ versus cigarette smoking (−), exercise habits (+)

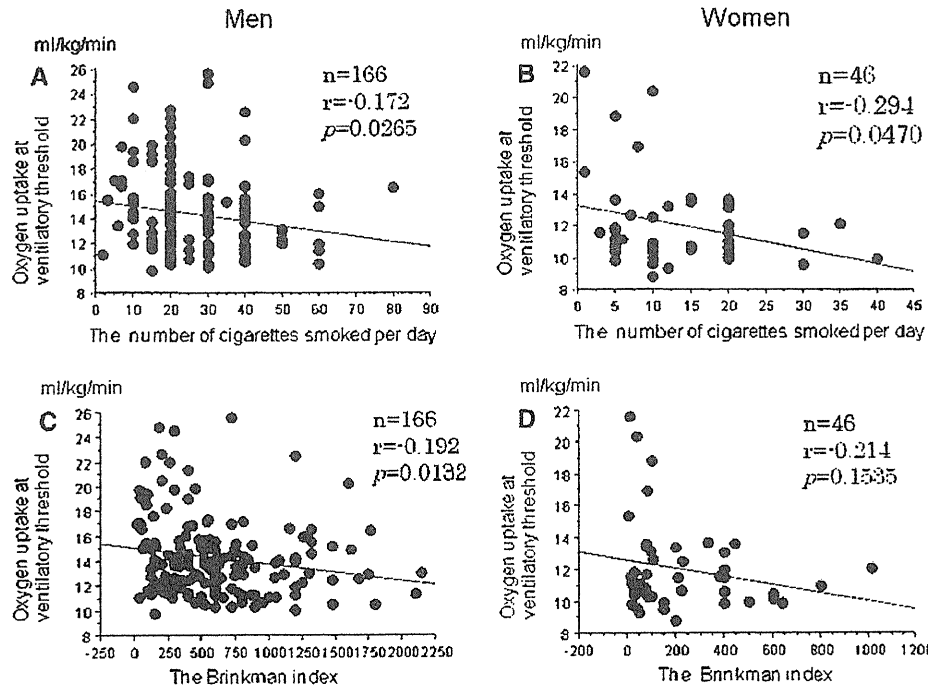

Fig. 1 Simple correlation analysis between the number of cigarettes smoked per day and oxygen uptake at ventilatory threshold (**a** men, **b** women), and between the Brinkman Index and oxygen uptake at ventilatory threshold (**c** men, **d** women)

among 1,393 men over 7 years. In this study, we solely evaluated the relationship between cigarette smoking and aerobic exercise level defined by VT in the Japanese. Exercise habits were closely linked to cigarette smoking in men, and the differences of parameters at VT between subjects with and without cigarette smoking were attenuated after adjusting for age and exercise habits. However, in women without exercise habits, oxygen uptake at VT in women with cigarette smoking was significantly lower than that in women without, after adjusting for age. In addition, we compared oxygen uptake at VT among subjects with and without cigarette smoking and exercise habits, and found that oxygen uptake at VT in group B was highest among four groups in men. Oxygen uptake at VT in group C was lowest among four groups in both sexes. Taken together, a combination of promoting exercise habits and prohibiting cigarette smoking might be considered for improving aerobic exercise level, especially in women.

Potential limitations still remain in this study. First, our study was a cross-sectional and not a longitudinal study. Second, 407 men and 418 women in our study voluntarily underwent measurements; they were therefore more likely to be health conscious compared with the average person. Third, we could not show a clear relation between cigarette smoking and oxygen uptake at VT. Fourth, the relationship between cigarette smoking and exercise habits was not noted in women. The low prevalence of subjects with exercise habits and cigarette smoking might affect the results. However, it seems reasonable to suggest that prohibiting smoking and promoting exercise habits might result in amelioration of aerobic exercise level in some Japanese. Sandvik et al. [21] reported that physical fitness was a graded, independent, long-term predictor of mortality from cardiovascular causes in healthy, middle-aged men. To show this, further prospective studies are needed in the Japanese.

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Relationship between work style and cigarette smoking in Japanese workers

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ABSTRACT

We investigated the link between work style (*i.e.* day work and shift work) and cigarette smoking in Japanese workers. We used data of 3,238 men (39.3 ± 10.5 years) and 5,111 women (37.1 ± 10.9 years), aged 20 - 59 years, by cross-sectional clinical investigation study. Work style *i.e.* day work and shift work, cigarette smoking, status of stress and stress coping were obtained by questionnaires by well-trained medical staff. A total of 227 men (7.0%) and 339 women (6.6%) were shift workers, and 1346 men (41.6%) and 649 women (12.7%) were current smokers. Work style was significantly linked to cigarette smoking, stress and stress coping after adjusting for age in women. In addition, the level of stress coping in subjects with cigarette smoking was significantly lower than that in subjects without cigarette smoking even after adjusting for age in women. However, these associations were not noted in men. Work style was critically associated with cigarette smoking in Japanese female workers.

Keywords: Work Style; Shift Work; Cigarette Smoking; Stress Coping

1. INTRODUCTION

Economic globalization needs continuous processing or operations around the clock to optimize manufacturing system. A 24-hour continuous operation system has become more popular and shift workers have become also more popular in Japan. Several reports have showed that shift work is associated with coronary artery disease [1], hyper cholesterolemia [2,3], weight gain [4] and hypertension [5].

Cigarette smoking is an important public health challenge, and it has been reported that 39.4% of men and 11.0% of women are current smokers in Japan [6]. Cigarette smoking is also a strong risk factor for atherosclerosis and cardiovascular disease in a dose-dependent manner [7]. However, the link between work style such as day work and shift work, and cigarette smoking in Japanese workers still remains to be investigated.

Therefore, in this study, we evaluated the link between work style and cigarette smoking and the effect of stress and stress coping on cigarette smoking in Japanese workers.

2. SUBJECTS AND METHODS

2.1. Subjects

We used data for 3238 Japanese male workers (39.3 ± 10.5 years) and 5111 women (37.1 ± 10.9 years), retrospectively from a database of 16,380 subjects who met the following criteria: 1) they had wanted to change their lifestyle *i.e.* diet and exercise habits, and had received an annual health check-up from June 1997 to Dec 2009 at Okayama Southern Institute of Health, 2) received evaluation of work style, cigarette smoking, status of stress and stress coping as part of the annual health check-up, 3) they were day workers and/or shift workers, aged 20 - 59 years, and 4) provided written informed consent (**Table 1**).

Ethical approval for the study was obtained from the Ethical Committee of Okayama Health Foundation.

2.2. Work Style

Subjects completed a self-administered questionnaire. This included the following question regarding patterns of work style: During your working life, until the present, what shift (time of day) did you work most: mainly day time, mainly night (*i.e.* fixed-night shift), or alternate

Table 1. Clinical profiles of enrolled subjects.

	Men	Women
Number of subjects	3238	5111
Age	39.3 ± 10.5	37.1 ± 10.9
Height (cm)	167.0 ± 5.8	157.2 ± 5.4
Body weight (kg)	71.2 ± 11.7	54.8 ± 9.2
Body mass index (kg/m^2)	24.6 ± 3.7	22.2 ± 3.6
Abdominal circumference (cm)	83.9 ± 10.2	70.3 ± 9.2
Hip circumference (cm)	94.6 ± 6.2	91.0 ± 6.1
		Mean ± SD

night and daytime (that is, rotating-shift work)? In this study, we excluded 65 male and 131 female night workers to evaluate the influence of shift work on cigarette smoking compare to day workers.

2.3. Exposure Data

The self-administered questionnaire also inquired about other characteristics of smoking status (never or current smoker), status of stress (yes or no) and stress coping (yes or no).

2.4. Anthropometric Measurements

The anthropometric parameters were evaluated by using the following respective parameters such as height, body weight, body mass index (BMI), abdominal circumference, hip circumference. BMI was calculated by weight/[height]^2 (kg/m^2). The abdominal circumference was measured at the umbilical level and the hip was measured at the widest circumference over the trochanter in standing subjects after normal expiration [8].

2.5. Statistical Analysis

Data are expressed as mean ± standard deviation (SD) values. A comparison of parameters was performed by χ^2 test and logistic regression analysis: $p < 0.05$ was considered to be statistically significant. Statistical analysis was performed with StatView 5.0 (SAS Institute Inc., Cary, NC, USA).

3. RESULTS

A total of 227 men (7.0%) and 339 women (6.6%) were shift workers, and the rate of shift workers was the highest in 20's in both sexes (**Table 2**).

Table 3 shows the comparison of cigarette smoking as classified by age group. Current smokers were decreased with age in both sexes, and 1346 men (41.6%) and 649 women (12.7%) were current smokers.

We also evaluated the status of stress (**Table 4**). 2071 men (64.0%) and 3,735 women (73.1%) women answered as having stress, and the rate of subjects with having stress was the highest in 30's in both sexes. However, subjects with having stress coping was comparably lower [1539 men (47.5%) and 2730 women (53.5%)] (**Table 5**). The rate of subjects with having stress coping was the highest in 20's in men and in 50's in women.

In addition, we evaluated the relationship between work style and cigarette smoking, status of stress and stress coping. In women, the rate of current smoker and having stress was significantly higher in shift workers than those in day workers after adjusting for age (**Table 6**). The rate of having stress coping in shift workers was significantly higher than that in day workers after adjusting for age. In men, those clear associations were not noted.

Finally, we investigated the relationship between cigarette smoking and status of stress and stress coping (**Table 7**). The rate of having stress coping in current smokers was significantly lower than that in non smokers even after adjusting for age in women, but not in men. The relationship between cigarette smoking and status of stress was not noted in both sexes.

4. DISCUSSION

We evaluated the link between work style and cigarette smoking in Japanese workers and we found that close associations between shift work and cigarette smoking in female workers. In addition, having stress coping might be important for Japanese female workers for prohibiting smoking.

In some literatures, work style was closely associated with cigarette smoking especially male workers. Fujino *et al.* reported that the rate of current smoker was higher in shift male workers (59.5%) than that in day male workers (55.4%) in Japan Collaborative Cohort Study for the Evaluation of Cancer Risk (JACC Study) [1]. Dochi *et al.* also reported that the rate of current smoker was higher in shift workers (68.8%) than that in day workers (58.8%) in male workers in steel company [2]. Suwazono *et al.* also showed that shift work was closely associated with cigarette smoking in male workers [4]. There were few studies that evaluated the relationship between shift work and cigarette smoking in Japanese female workers. Kageyama *et al.* reported that the prevalenve of current smoker was 29%, being higher than that in the general population of Japanese women by evaluating 522 Japanese female staff nurses [9]. In this study, it is note worthy that we found the relationship between work style and cigarette smoking in women even after adjusting for age. However, those associations were not noted as previous study in men. Enrolled subjects in this study were undertaken health check-up and they wanted to change their lifestyle. Therefore close associations might not be noted in men.

According to the relation between work style and status of stress, 3-shift system of employment increases work-related stress [10]. Parkes carried out cross-sectional

Table 2. Comparison of work style as classified by age group.

	Men				Women			
	Day work	%	Shift work	%	Day work	%	Shift work	%
20 - 29	661	90.4	70	9.6	1575	90.0	175	10.0
30 - 29	888	92.6	71	7.5	1135	93.5	79	6.5
40 - 49	790	93.7	53	6.3	1207	95.3	59	4.7
50 - 59	672	95.3	33	4.7	855	97.0	26	3.0
Total	3011	93.0	227	7.0	4772	93.4	339	6.6

Table 3. Comparison of cigarette smoking as classified by age group.

	Men				Women			
	Cigarette smoking (+)	%	Cigarette smoking (–)	%	Cigarette smoking (+)	%	Cigarette smoking (–)	%
20 - 29	329	45.0	402	55.0	281	16.1	1469	83.9
30 - 29	413	43.1	546	56.9	179	14.7	1035	85.3
40 - 49	349	41.4	494	58.6	130	10.3	1136	89.7
50 - 59	255	36.2	450	63.8	59	6.7	822	93.3
Total	1346	41.6	1892	58.4	649	12.7	4462	87.3

Table 4. Comparison of stress as classified by age group.

	Men				Women			
	Stress (+)	%	Stress (–)	%	Stress (+)	%	Stress (–)	%
20 - 29	443	60.6	288	39.4	1297	74.1	453	25.9
30 - 29	645	67.3	314	32.7	925	76.2	289	23.8
40 - 49	566	67.1	277	32.9	910	71.9	356	28.1
50 - 59	417	59.1	288	40.9	603	68.4	278	31.6
Total	2071	64.0	1167	36.0	3735	73.1	1376	26.9

Table 5. Comparison of stress coping as classified by age group.

	Men				Women			
	Stress coping (+)	%	Stress coping (–)	%	Stress coping (+)	%	Stress coping (–)	%
20 - 29	377	51.6	354	48.4	957	54.7	793	45.3
30 - 29	419	43.7	540	56.3	642	52.9	572	47.1
40 - 49	405	48.0	438	52.0	631	49.8	635	50.2
50 - 59	338	47.9	367	52.1	500	56.8	381	43.1
Total	1539	47.5	1699	52.5	2730	53.4	2381	46.6

Table 6. Relationship between work style and cigarette smoking, stress and stress coping.

Men	Cigarette smoking (+)	Cigarette smoking (–)	*p*	*p* (After adjusting for age)
Day work	1248	1763	0.6113	0.7664
Shift work	98	129		
	Stress (+)	Stress (–)		
Day work	1924	1087	0.7950	0.8360
Shift work	147	80		
	Stress coping (+)	Stress coping (–)		
Day work	1419	1592	0.0951	0.1054
Shift work	120	107		
Women	Cigarette smoking (+)	Cigarette smoking (–)		
Day work	574	4198	**<0.0001**	**<0.0001**
Shift work	75	264		
	Stress (+)	Stress (–)		
Day work	3444	1328	**<0.0001**	**<0.0001**
Shift work	291	48		
	Stress coping (+)	Stress coping (–)		
Day work	2505	2267	**<0.0001**	**<0.0001**
Shift work	225	114		

Table 7. Relationship between cigarette smoking and stress, stress coping.

Men	Stress (+)	Stress (–)	*p*	*p* (After adjusting for age)
Cigarette smoking (+)	840	506	0.1208	0.1053
Cigarette smoking (–)	1231	661		
	Stress coping (+)	Stress coping (–)		
Cigarette smoking (+)	602	744	**0.0070**	0.1054
Cigarette smoking (–)	937	955		
Women	Stress (+)	Stress (–)		
Cigarette smoking (+)	496	153	**0.0396**	0.0797
Cigarette smoking (–)	3239	1223		
	Stress coping (+)	Stress coping (–)		
Cigarette smoking (+)	321	328	**0.0307**	**<0.0001**
Cigarette smoking (–)	2409	2053		

research targeting 736 two-shift workers and 1131 day workers at an oil refinery, and concluded that the 2-shift workers had higher job demand and less job control over their work [11]. In female workers, Kageyama *et al.* reported that the cigarette smoking-dependent tendency was associated with recent life events and the presence of insomnia [9]. Stress is probably the most important contributor to excess smoking levels [12]. American study showed that officers who smoked experienced high-stress levels more than twice that of non smokers [13]. Therefore, stress coping may important for prohibiting cigarette smoking. Serxner *et al.* recommended that smoking cessation and prevention programs should focus on change in individual coping mechanisms [14]. We also found that the rate of stress in shift smokers was higher than that in day workers and the rate of stress coping was also higher in shift workers than that in day workers after adjusting in women. Although the rate of stress coping was higher in shift workers than that in day workers, the rate of stress coping was significantly lower than in current smokers than that in non smokers in women. Taken together, it seems reasonable to suggest that simply recommending proper stress coping except cigarette smoking, might result in decreased cigarette smoking in some Japanese female workers.

Potential limitations remain in this study. First, our study was a cross sectional and not a longitudinal study. Second, the 3238 Japanese male workers and 5111 women, all of whom wanted to change their lifestyle, underwent measurements for this study: they were therefore more health-conscious than the average person. In fact, in men, clear associations were not noted the relationship between shift work and cigarette smoking as previous studies [1,2,4]. Third, we could not obtain the data of the average number of cigarettes smoked per day or subject' age when they started smoking. Subjects who smoked before the date of the analysis but who had stopped by then would have therefore been categorized as non-smokers. Fourth, status of stress and stress coping was evaluated by simple questionnaire (yes or no). Therefore, further prospective studies are needed in Japanese workers to prove the link between work style and cigarette smoking.

5. CONFLICT OF INTEREST

There is no conflict of interest.

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REVIEW ARTICLE

Use of "AminoIndex Technology" for Cancer Screening

Naoyuki Okamoto

REVIEW ARTICLE Ningen Dock 2012 ; **26** : 911-922

Use of "AminoIndex Technology" for Cancer Screening

Naoyuki Okamoto

Amino acids play a central role in many biological activities. Several recent studies have reported that plasma amino acids can be used as biomarkers to assess disease risk or progression, or to select proper treatment. This review summarizes recent clinical research using a novel approach of multivariate analysis called "AminoIndex Technology", which is based on plasma amino acids profile for cancer screening. A multicenter study was conducted to explore and validate the application of "AminoIndex Technology" to cancer screening for gastric, lung, colorectal, prostate, and breast cancers. AminoIndex® Cancer Screening (AICS) scoring involves evaluating cancer based on amino acid concentrations using 5 types of AICS values. AICS enables simultaneous testing for multiple cancers regardless of cancer or tissue type. Furthermore, because AICS can detect stage II (stage B) or earlier cancers and can easily be performed on a plasma sample, it can be conducted in conjunction with comprehensive medical examinations or regular health check-ups. It is expected that "AminoIndex Technology" will be applied to cancer screening and various other areas of clinical utility.

Key Words : plasma amino, cancer screening, multivariate analysis, biomarker

Amino acids are usually considered protein subunits or nutrients. However, recent advances in the metabolomics of amino acids and high-throughput analytical techniques have shown that amino acids in the body (e.g. in the blood) can be used as biomarkers for evaluating disease risk or progression and for selecting proper treatment. For example, one study has reported that the risk of developing diabetes mellitus can be predicted from the metabolite profiles of a combination of 3–5 amino acids in the blood[1]. These new biomarkers, which are derived from combinations of amino acid concentrations, allow prediction of the risk of developing diabetes mellitus even when adjusted for conventional insulin resistance-related indices such as fasting insulin levels, homeostatic model assessment of risk of insulin resistance, and a 75-g oral glucose tolerance test. Amino acid metabolism indices differ from conventional biochemical indices and therefore may be regulated by a different paradigm. I anticipate that further research into amino acid metabolism will provide new information about disease risk and progression.

Advances in analytical techniques are among the most important reasons why novel findings concerning amino acid metabolism, such as the ability to predict the risk of developing diabetes, have been reported over the last several years. Plasma amino acid concentrations have conventionally been measured using an amino acid autoanalyzer that combines ion-exchange chromatography and a ninhydrin reaction. However, this method is so time-consuming that it has been used only for specific purposes, such as clinical studies with limited blood samples or in the diagnosis of inborn errors of metabolism. Progress

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in amino acid analysis techniques has led to using liquid chromatograph mass spectrometry (LC-MS) more frequently than the conventional method and analysis using LC-MS has enabled high-throughput measurement of plasma amino acids. Moreover, with the spread of this technology an enormous database of information is now available and it provides many clinically important insights into amino acid metabolism. As a result, many new amino acid metabolism findings have recently been reported.

In this review, I will first briefly discuss the role of plasma amino acids in the body and then summarize recent clinical research using novel plasma amino acid biomarkers for cancer screening.

Functions of amino acids in the body

Amino acids account for approximately 20% of an individual's body weight so a 50 kg person has approximately 10 kg of amino acids, most of which exist as proteins (**Fig. 1**). Free amino acids, known as the amino acid pool, are found in cells, intercellular components, plasma, and other biological components. Amino acids, which are digested and absorbed from foods and then enter the amino acid pool, from which they are used for protein synthesis, and are later returned to the amino acid pool as a result of protein degradation or excreted in the urine or feces. In this turnover process, the body replaces its protein composition through metabolism every 2–3 months.

The concentration of free amino acids in the plasma, which is part of the amino acid pool, is precisely regulated by a variety of control mechanisms and is maintained at a constant level in healthy individuals. Many studies have shown that various disease states, such as hepatic or renal failure, Alzheimer's disease, psychological disorders, and inflammatory bowel disease, may alter the plasma amino acid balance through aberrations in these regulatory mechanisms[2-6]. Also, as amino acid metabolism occurs actively in the muscle, the liver, the brain, the kidney, and the small intestine, changes in the amino acid metabolism balance in these organs are reflected as changes in the plasma amino acid concentrations.

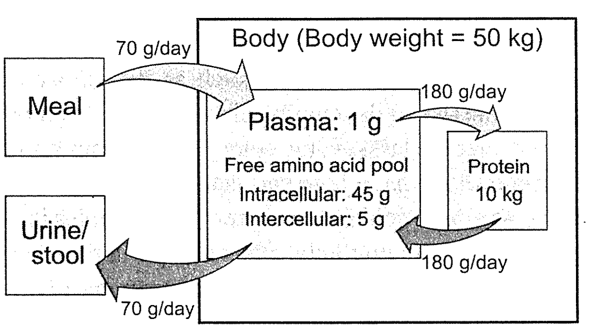

Fig. 1. Amino acid and plasma free amino acid pool in body

Metabolomics research and "AminoIndex Technology"

Recent advances in analytical techniques have enabled disease states to be analyzed through the comprehensive measurement of metabolites[1]. However, problems remain in the clinical setting with regard to the reproducibility, quantification, and cost of this type of analysis. The approach to such analysis using "AminoIndex Technology" is based on the assessment of diseases and physical conditions using plasma amino acid concentrations obtained through the measurement of a particular subset of metabolites. Measurement of amino acid metabolites is particularly useful for predicting various conditions because amino acid metabolism is closely related to many other metabolic pathways, such as glucose and lipid metabolism, and amino acids can therefore be considered as "hubs" to which many types of metabolites on the metabolic map are connected.

So the measurement of amino acid levels enables us to infer the statuses of various aspects of the overall metabolic map, such as those of glucose or lipid metabolism. In the previously mentioned study using metabolites as a measure of the risk of developing diabetes, an assay of 61 metabolites resulted in the identification of 3 or 5 metabolites associated with disease risk, all of which were amino acids. The underlying concept of "AminoIndex Technology" is to focus on these amino acids and to establish a reproducible and quantifiable method of measurement with applications in the clinical setting.

"AminoIndex Technology" is a technique in which multivariate analysis of the plasma amino acid concentration (**Fig. 2**) is used to compute disease or health condition scores. Through the use of statistical models, it can be used to predict the detection or severity of a single disease and clarify the status of multiple diseases or health conditions from a single blood sample. Recent research using "AminoIndex Technology" has been reported in other areas[7,8] in addition to the cancer studies reported in this review, and their clinical utility has been summarized in another review[9].