厚生労働科学研究費補助金

循環器疾患・糖尿病等生活習慣病対策総合研究事業

糖尿病・メタボリックシンドロームにおける内臓脂肪蓄積の評価に関する疫学研究

（ H20-糖尿病等-若手-003 ）

平成20年度～22年度　総合研究報告書

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糖尿病・メタボリックシンドロームにおける内臓脂肪蓄積の評価に関する疫学研究(H20-糖尿病等-若手-003)

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研究要旨　日本のメタボリックシンドローム診断基準では、腹囲カットオフは男性85cm、女性90cmである。国際基準との整合性や疾病発症との関連性を含めいくつか課題も指摘されている。腹囲はメタボリックシンドロームの上流に位置づけられる内臓脂肪の簡易指標であることを考えると、まずは内臓脂肪蓄積と諸病態との関連を解明しておく必要があろう。本研究は、糖尿病・メタボリックシンドローム、及び関連する病態における内臓脂肪蓄積の意義を明らかにすることを目的とする。このことによりメタボリックシンドローム診断基準を改訂する際に参考となる腹囲に関する知見を提供する。

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A. 研究目的

腹部CTにて計測した内臓脂肪面積と、インスリン抵抗性、メタボリックシンドローム、高血圧、糖尿病、脳心血管イベント、さらにはバイオマーカーとの関連を疫学的に明らかにする。この結果に基づき疾病リスクが高まる内臓脂肪面積の閾値を男女別に判定し、該当する腹囲を求める。内臓脂肪蓄積を基盤に耐糖能異常、脂質代謝異常、血圧高値をきたし、その状態が継続することにより、高血圧、糖尿病、さらには脳心血管疾患のリスクが高まるメタボリックシンドロームが世界的に注目されている。日本の腹囲基準は、腹部 CT で測定した内臓脂肪面積 $100cm^2$ に相当する値であり、男性より女性の方が大きいという特徴がある。申請者らは感度・特異度分析により、女性の現腹囲基準（90cm 以上）を用いた場合の問題点を指摘したが (Matsushita Y, et al. Diabetes Care. 5:1123-1124, 2006)、メタボリックシンドロームの発症機序を考えると、その上流にある内臓脂肪を正確

に把握した上で、インスリン抵抗性をはじめとする諸病態との関連を解明する必要がある。また、内臓脂肪の簡易指標である腹囲を診断的に補うバイオマーカーの検索も必要であろう。職域人間ドックで CT を行う受診者について、内臓脂肪面積とインスリン抵抗性、高血圧、糖尿病、脳心血管イベントとの関連を断面的、及び経時的に検討する。また、内臓脂肪蓄積を反映するバイオマーカーを測定し、その予防医学的な有用性を評価する。これらの病態のリスクが急激に変化する内臓脂肪面積の閾値を男女別に判定し、該当する腹囲を推定する。

B. 研究方法

対象：

日立製作所日立健康管理センタで通年行われている人間ドック成績のうち、腹部ＣＴ検査が導入された平成16年度以降を分析対象とした。さらに、平成20年度以降の受診者には同意を得た上で研究用の追加採血を行った。本研究は同社の産業医との共同研究として進めることで合意しており、国立国際医療研究センター、日立製作所の両施設において倫理審査委員会の承認を得た。

同センタ人間ドックでは、中性脂肪、HDL コレステロール、血圧、空腹時血糖、腹囲といったメタボリックシンドローム診断に必要な項目に加え、インスリンや高感度 CRP が受診者全員について測定されている。腹部 CT による内臓脂肪面積の計測は希望者に行われているが、人間ドック受診者 17,000 人の約 3 分の 1 にあたる 6,000 人が毎年、腹部 CT を受診している。なお、人間ドック受診者における男女比は 6：1 である。

方法：

1. 研究のセットアップ
   日立健康管理センタ産業医との共同研究として進めることで合意し、国立国際医療研究センター、日立製作所の両施設において倫理審査委員会の承認を得た上で、研究を開始した。作業手順書を作成し、現場で円滑に研究が遂行できるようにした。
2. 既存の人間ドックデータ（平成 16 年～平成 20 年）のデータベース化
   コーディングマニュアルを作成した。元データを連結可能匿名化し、解析用データベースを完成した。糖尿病、高血圧、高脂血症、脳心血管疾患の既往歴、治療の有無は人間ドックの調査票および欠勤時の診断書より把握した。(ICD10 コードによる分類を行った。)
3. 採血およびアディポネクチンの測定
   (同意書の得られた人のみ)
   人間ドック受付時に研究用採血についての説明・依頼文書と同意書を渡し、書面で同意を得た。同意の得られた人から静脈血 5ml を採取し、同施設にてアディポネクチンを測定した（約 9,000 名の測定を終了した)。残検体は健診施設内の冷凍庫（－80℃）に一時保管し、1 ヶ月ごとに国立国際医療研究センターへ低温で輸送し、凍結保管（－80℃）した。

（倫理面への配慮）

本研究の実施計画は「疫学研究に関する倫理指針」に則って作成し、研究実施前に、研究代表者及び実施する会社の分担研究者は研究計画書をそれぞれが所属する機関の倫理委員会に諮り、承認を得た。通常に行われている健診データの使用にあたっては、個別にインフォームドコンセント

をとらず、社内の掲示にて研究の目的と意義を説明した。また研究用採血に関して、調査内容をわかりやすく示したパンフレットを用いて、自由意志に基づく参加であることや個人情報の保護対策を含め人間ドックスタッフが対象者に説明した後に、本人から署名入りの同意書を得た上で実施した。人間ドック検査成績と採取した血液は匿名化（連結可能）した上で、鍵のかかるロッカー、－80℃の冷凍庫にそれぞれ保管した。結果の公表に際しては個人が特定できない形式で行った。

C. 研究結果

1) 内臓脂肪面積をはじめとする各体格指数がメタボリックシンドロームのリスク重積に及ぼす影響

腹部 CT 受診者 6,292 名（男性 5,606 名、女性 686 名）を対象として、CT による内臓脂肪面積、皮下脂肪面積、腹囲、BMI とメタボリックシンドロームのリスク重積のオッズ比を、各体格指数ごとに 5 分位に分け、比較した。腹囲測定は CT 測定による内臓脂肪面積に比べ、メタボリックシンドロームのリスク重積を女性では 5 割、男性では 7 割しか検出することができず、内臓脂肪蓄積の簡易指標として腹囲を用いることに限界があることを明かにした（Matsushita Y, et al. Diabetes Care. 33: 2117-2119, 2010)。

2) 禁煙期間と内臓脂肪面積・メタボリックシンドロームの関係

禁煙後の体重増加はメタボリックシンドロームなどの代謝性疾患のリスク上昇に繋がる可能性がある。その際、これが禁煙後の期間との間にどのような関係があるのか、また、内臓脂肪や皮下脂肪の変化がそれにどのように影響するのかについて、現状では明確な見解は得られていない。そこで、腹部 CT 検査を行った 5,697 名の男性（年齢 52.7 歳，BMI 24.1 kg/m^2，内臓脂肪面積 124.0 cm^2；いずれも平均値）を対象として、喫煙歴のない非喫煙者を基準にし、メタボリックシンドロームとその要因の有無の OR を過去喫煙者（禁煙後 4 年以内、5～9 年、10～14 年、15 年以上）および現在喫煙者の群で求めた。年齢、飲酒、定期的な運動の有無によって調整したロジスティック回帰分析を用いた（Matsushita Y et al. Obesity. 19: 647 -651, 2011)。

その結果、喫煙状況別にみると、現在喫煙者の内臓脂肪面積の平均値が 120.4 cm^{2}と最も低く、過去喫煙者（124.0～132.0 cm^2）は非喫煙者（123.1 cm^2）に比べ、内臓脂肪面積が多かった。過去喫煙者の内臓脂肪面積は禁煙後の期間が長くなるにしたがって減る傾向があり、15 年以上禁煙すると内臓脂肪面積は非喫煙者とほぼ同等になることが明らかになった。

メタボリックシンドロームの有無の非喫煙者に対するORは、現在喫煙者で1.02、禁煙後4年以内、5～9年、10～14年、15年以上の過去喫煙者ではそれぞれ1.33、1.36、1.40、1.09であった。これらを内臓脂肪面積でさらに調整すると、禁煙後15年未満の過去喫煙者のオッズ比は35～55.6%減少したが、皮下脂肪面積による調整ではそのような事象は認められなかった。禁煙後は、内臓脂肪面積が増加しないように身体活動を増やし、摂取エネルギー量を適正に保つことが必要である。現在喫煙者は、15年以上禁煙することにより、メタボリックシンドロームのリスク重積

が非喫煙者と同等まで減少するので、15年以上の地道な禁煙が必要である。

3) 腹囲測定部位とメタボリックシンドローム

メタボリックシンドロームの診断基準では、内臓脂肪蓄積の簡易指標として腹囲が使われているが、腹囲は測定方法によって誤差が出やすい問題があり、また、その測定部位は国際的にも統一されていない。そこで、腹囲について，1,140名（男性969名，女性171名）を対象に，世界で使用されている代表的な腹囲の4部位（①最も細い部位②肋骨弓下線端と前腸骨稜上線の中点③臍位④前腸骨稜上線）を測定し，メタボリックシンドロームのリスク重積を予測するうえで最適な部位をROC曲線を描き，検討した。(Matsushita Y et al. Obesity 18: 2374-2378, 2010)。

その結果，腹囲の最大値と最小値の差の平均は，男性では3.9cmであったが，女性では12.6cmであり，測定部位による大きな差が女性で認められた。また、各腹囲測定部位によるメタボリックシンドロームの予測能力に有意差は認められないことが明らかになった。さらに，アジアにおける腹囲のメタボリックシンドローム診断基準である男性 90cm，女性80cmをカットオフ値として，リスク重積の感度，特異度を各測定部位で比較したが，感度，特異度いずれも相当のばらつきが認められた。

今回の研究より、各メタボリックシンドロームの診断基準で定められた腹囲測定部位で正確に測定することが必要であることが示唆された。また，今後、メタボリックシンドロームの頻度などを国際的に比較検討していくためには，測定部位の国際的な統一が望ましい。

4) アディポネクチン・内臓脂肪面積がメタボリックシンドロームのリスク重積に及ぼす影響

男性6,221名、女性775名、合計6,996名を対象とし、アディポネクチン、内臓脂肪面積別にそれぞれ4分位、16群に群分けし、アディポネクチン最高値・内臓脂肪面積最低値群を基準（1.0）とした時のメタボリックシンドロームのリスク重積の調整オッズ比を求めた。アディポネクチン最低値・内臓脂肪面積最高値群が最も高いオッズ比（95%信頼区間）であった（男性：12.7 (9.7-16.6)、女性：13.5 (6.0-30.2)）。

D. 考察

横断解析により、内臓脂肪蓄積が多いほど、メタボリックシンドロームのリスク重積が高まることが明らかになった。また、腹囲測定はCT測定による内臓脂肪面積に比べ、メタボリックシンドロームのリスク重積を女性では5割、男性では7割しか検出することができず、内臓脂肪蓄積の簡易指標として腹囲を用いることに限界があることが明かになった。さらに、年齢別にみると、内臓脂肪面積とBMI、腹囲の動きは必ずしも一致しないことがわかり、現在、メタボリックシンドロームの腹囲カットオフは年齢別には示されていないが、年齢も考慮する必要があると考えられる。

縦断解析では、内臓脂肪面積の3年間の増加を50 cm^2未満に抑制することにより、メタボリックシンドロームのリスク

重積の解消につながる可能性が示唆された。

アディポネクチンは脂肪細胞が出すホルモンの一つで動脈硬化を防いだり、脂肪酸の燃焼を促したりする働きがあることが動物実験で分かっているが、今回、ヒトで同じ内臓脂肪の付き方でもアディポネクチン量によりメタボリックシンドロームのリスク重積が異なる事が明らかになった。

また、現在喫煙者が、15年禁煙することにより、メタボリックシンドロームのリスク重積が、非喫煙者と同等まで減少することが明らかになった。

E. 結論

得られたデータは、前向きコホート研究による発症率調査及び糖尿病・メタボリックシンドロームの曝露要因としての役割の検討の際、基礎データとして活用する。

横断解析、縦断解析により、内臓脂肪面積の重要性が明らかになり、また、同じ内臓脂肪面積でもアディポネクチンの量により、メタボリックシンドロームのリスクが大きく異なることが明らかになった。

今後は現在、申請者らが開発中である内臓脂肪の蓄積をより鋭敏に反映する効果的、経済的で簡便に測れる評価モデル式を身体計測値とバイオマーカー、生活習慣要因からさらに検討し、推定能力の高いものに改訂する。さらに、その式が循環器疾患リスクを予測できるかどうかについて10年間の追跡を行い、妥当性を検討する。エンドポイントは、高血圧、糖尿病、高脂血症、メタボリックシンドローム、心電図異常、心臓足首血管指数（CAVI）、さらに症例数が解析可能な数に達し時点で脳心血管イベントとする。

F. 研究発表

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加藤隆則、大内崇徳、岡田佳之、中川徹、色川正貴、松下由実
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8) ウエスト測定部位ごとのメタボリックシンドロームのリスクファクター重積予測能力
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(第21回日本疫学会学術総会　北海道 平成23年1月)

国際学会

禁煙とメタボリックシンドローム:日立健康研究
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(Asia Pacific Conference on Health Promotion and Education 千葉　平成21年7月)

シンポジウム開催

「おなかによく効く市民公開講座　メタボ退治にどう立ち向かうか？！　－目からウロコの“はらいい”ばなし」
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G. 知的財産権の出願・登録状況
1) 特許取得
　なし
2) 実用新案登録
　なし
3) その他
　なし

研究成果の刊行に関する一覧表

書籍

著者氏名	論文タイトル名	書籍全体の編集者名	書　籍　名	出版社名	出版地	出版年	ページ
野田光彦	健診結果の生かし方	矢冨裕、 野田光彦	新 健康診断と検査がわかる本　健康診断と検査結果を生かす	時事通信社	東京	2008	8-9
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野田光彦	「糖尿病とメタボリックシンドローム」サイトマップ	近藤達也、山西文子、野田光彦	生活習慣病看護エッセンスブック 第8~11巻 糖尿病とメタボリックシンドローム1	メジカルフレンド社	東京	2008	各巻iv-v
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Visceral Fat Area and Markers of Insulin Resistance in Relation to Colorectal Neoplasia

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OBJECTIVE — Although abdominal obesity and related metabolic abnormalities are hypothesized to promote colorectal carcinogenesis, direct confirmation of this effect is required. Here, we examined the relation of early-stage colorectal neoplasia to visceral fat area and markers of insulin resistance.

RESEARCH DESIGN AND METHODS — Subjects were participants in a comprehensive health screening conducted at the Hitachi Health Care Center, Ibaraki, Japan. During a 3-year period (2004–2007), a total of 108 patients with early-stage colorectal neoplasia, including 22 with early cancer, were identified among individuals who received both colorectal cancer screening and abdominal computed tomography scanning. Three control subjects matched to each case subject were randomly selected from those whose screening results were negative. Conditional logistic regression analysis was used to examine the association of measures of obesity and markers of insulin resistance with colorectal neoplasia, with adjustment for smoking and alcohol drinking.

RESULTS — Visceral fat area, but not subcutaneous fat area, was significantly positively associated with colorectal cancer, with odds ratios (95% CI) for the lowest to highest tertile of visceral fat area of 1 (reference), 2.17 (0.45–10.46), and 5.92 (1.22–28.65), respectively (P_{trend} = 0.02). Markers of insulin resistance, particularly fasting glucose, were also positively associated with colorectal cancer risk. In contrast, no associations were observed for colorectal adenomas.

CONCLUSIONS — These results suggest that visceral adipose tissue accumulation and insulin resistance may promote the development of early-stage cancer but not adenoma in the colorectum.

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Although the role of obesity as a strong predictor of various chronic diseases, including type 2 diabetes and cardiovascular disease, has been established, accumulating evidence also indicates the importance of obesity and its related metabolic disorders in the development of cancer (1). In Japan, the incidence of colorectal cancer has sharply increased over the last several decades and is now among the highest in the world (2). This time trend, as well as findings from migrant studies (3), suggests the involvement of environmental factors in colorectal carcinogenesis. Epidemiological studies (4,5) have shown that colorectal cancer risk is more strongly associated with waist circumference than with BMI, indicating the etiological importance of abdominal or visceral fat disposition, rather than overall adiposity. However, given that waist circumference is only a surrogate of visceral fat mass, more direct evidence is required before the link between visceral adiposity and cancer risk can be considered conclusive.

Several studies have assessed the association between visceral fat area, as measured using computed tomography (CT) scanning, and colorectal neoplasia (6–10), but results have been mixed. For example, a Japanese study (7) demonstrated an increased prevalence of colorectal adenomas among individuals with higher visceral fat area, whereas a larger, more recent study (8) did not. Given that adenomatous polyps are common but only a minority progress to cancer (11), the association with cancer should also be explored, but evidence to date is sparse. In a Turkish study (10), patients with colorectal cancer tended to have a smaller rather than larger visceral fat area than that in control subjects. This unexpected finding may have been due to weight loss in the course of cancer development, however, a possibility that highlights the importance of assessing visceral fat before the diagnosis of cancer or development of symptoms.

An insulin hypothesis has been proposed to explain the observed association between obesity or abdominal obesity and colorectal neoplasia (12,13). Accumulation of visceral fat is a strong determinant of insulin resistance and hyperinsulinemia (14) and, as experimental data show (15), insulin promotes colorectal carcinogenesis. Compatible with the insulin hypothesis, epidemiological data appear consistent in showing a positive association between colorectal neoplasia and markers of hyperinsulinemia or insulin resistance (rev. in 16). These findings notwithstanding, however, a role for insulin resistance in promoting the development of adenoma, cancer, or both in the colorectum has yet to be confirmed. To further explore these issues, we examined the relation of visceral fat mass assessed by CT and measures of insulin resistance to adenoma and cancer in the colorectum among asymptomatic individuals who underwent screening.

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RESEARCH DESIGN AND METHODS— Study subjects were participants in a comprehensive health examination conducted at the Hitachi Health Care Center, Ibaraki, Japan, during which colorectal cancer screening and, on request, abdominal CT scanning were performed. Abdominal CT scanning was introduced to encourage changes in lifestyle, such as diet and physical activity, by showing examinees a graphic image, together with estimated data, of their own abdominal fat accumulation. In practice, it was offered mainly to individuals who underwent chest CT scanning for the screening of lung cancer. Nearly one-third of all individuals who underwent screening chose to receive abdominal CT assessment. Compared with men who did not, those who underwent abdominal CT scanning were older (53 vs. 46 years), were more likely to be past smokers (35 vs. 22%), and tended to have a higher BMI (23.9 vs. 23.6 kg/m^2). In contrast, the two groups were similar in terms of alcohol drinking (> 1 *go* [23 g ethanol]/day: 32 vs. 29%). A *go* is a conventional unit of alcohol intake in Japan.

During the 3-year period from April 2004 to March 2007, 47,224 examinees underwent fecal occult blood testing, which is specified as the standard procedure for colorectal cancer screening in the Japanese guidelines. Owing to limitations in colonoscopy resources, individuals with a positive blood test were first invited to receive a barium enema in the health center, and only those with suspected polyp lesions were referred to a medical specialist for detailed examination by colonoscopy. Of 3,521 (8%) who had a positive test result, half (1,738) underwent barium enema at the center. Of these, 491 (28%) with a finding suggesting colorectal neoplasia were referred to local clinics or hospitals for confirmation. Of the 280 patients who were notified by the physicians consulted that they had colorectal neoplasia, the present case series consisted of the 86 with histologically confirmed adenoma and 22 with early-stage colorectal cancer (carcinoma in situ or cancer invading within the submucosa) who received abdominal CT scanning at the time of the health checkup. Among patients with adenomas of known size (n = 82), the number with adenomas of ≥10 mm in diameter was 15 (18%). Regarding the location of cancer, 5 cases were in the ascending colon, 2 were in the transverse colon, 13 were in the sigmoid colon, 1 was in the rectum, and 1 was not specified. For each case subject, three control subjects matched by year of examination, sex, and age (same age) were randomly selected from among examinees who had undergone abdominal CT measurement and had a negative fecal occult blood test. No case or control subject had a prior history of cancer, cardiac infarction, or stroke. Informed consent was obtained from each examinee regarding the use of his or her data for research purposes. The protocol of the present study was approved by the ethics committee of the Hitachi Health Care Center.

Abdominal CT measurement

Measurement of abdominal fat area with a CT scanner has been detailed elsewhere (17). In brief, single slice imaging was done at the level of the umbilicus in the supine position using a Redix Turbo CT scanner (Hitachi Medico, Tokyo, Japan). Imaging conditions, which have changed since 2004, were 120 kV, 50 mA, and a 5-mm slice thickness. Visceral fat area, subcutaneous fat area, and waist circumference were calculated using the PC software application fatPointer (Hitachi Medico).

Subject characteristics and blood measurements

Height and weight were measured using an automated scale (Tanita BF-220) with the patient wearing a light gown. BMI was calculated as the weight in kilograms divided by the square of height in meters. Fasting plasma glucose was measured by the glucose electrode technique using an ADAMS Glucose GA-1170 (Arkray). Fasting serum immunoreactive insulin (microunits per milliliter) was determined by an immunoenzymatic method using the AxSYM insulin assay (Abbott). Homeostasis model assessment of insulin resistance (HOMA-IR), an index of insulin resistance, was calculated as fasting glucose multiplied by fasting insulin divided by 405.

Covariates

Health-related lifestyles were ascertained by questionnaire. Participants entered their responses to the questionnaire directly into a computer using a custom-designed data entry system. Regarding smoking, the questionnaire inquired about smoking status and for ever-smokers it inquired about the duration and intensity of smoking. For alcohol consumption, the frequency of drinking and the amount of alcohol consumed per session was assessed in terms of *go*. One *go* contains ~23 g ethanol.

Statistical analysis

Subject characteristics were compared between case subjects with adenomas and their matched control subjects and between case subjects with cancer and their matched control subjects. In control subjects, Pearson correlation coefficients were calculated to examine the linear associations between visceral fat area and other exposure variables. Conditional logistic regression was used to assess the association of various obesity indexes (abdominal total fat mass, visceral fat area, subcutaneous fat area, waist circumference, and BMI) and measures of insulin resistance (insulin, glucose, and HOMA-IR) with colorectal neoplasia. Odds ratios (ORs) and 95% CIs for the prevalence of colorectal adenoma or cancer were calculated for the second and third (highest) tertiles of exposure, with the lowest tertile used as reference. Cutoff values for the exposure tertile were determined based on the distribution among control subjects for colorectal adenomas and cancer, respectively. Analyses were performed with and without adjustment for smoking (lifetime nonsmoker, ever-smoker with 1–600 cigarette-years, or ever-smoker with >600 cigarette-years), and alcohol consumption (nondrinker, drinker consuming ≤1 *go*/day, or drinker consuming >1 *go*/day). In analyses for the relation of insulin resistance to visceral fat area and blood markers, additional adjustment was also done for BMI. All analyses were performed using SAS (version 10; SAS Institute, Cary, NC). Two-sided $P < 0.05$ was considered statistically significant.

RESULTS— Table 1 shows patient characteristics for colorectal adenoma and cancer and their respective control subjects. Patients with colorectal adenomas were more likely to smoke and consume alcohol heavily than their matched control subjects. In contrast, they had levels of obesity and markers of insulin or insulin resistance similar to those of control subjects. Patients with colorectal cancer were more likely to be smokers and alcohol drinkers than their matched control subjects and on average had a greater BMI, waist circumference, and visceral and subcutaneous fat area than control subjects. Markers of insulin resistance were higher among patients with colorectal cancer than among their matched control subjects. In control subjects, visceral

Table 1—*Characteristics of study subjects*

	Colorectal adenoma		Colorectal cancer	
	Case subjects	Control subjects	Case subjects	Control subjects
n	86	258	22	66
Sex (% women)	3.5	3.5	4.6	4.6
Age (years)	54.0 ± 6.4	54.0 ± 6.4	53.8 ± 7.9	53.8 ± 7.7
Smoking (%)				
Lifetime nonsmoker	15.1	26.0	13.6	21.2
≤600 cigarette-years	38.4	36.1	45.5	39.4
>600 cigarette-years	46.5	38.0	40.9	39.4
Alcohol use (%)				
Nondrinker	24.4	26.7	22.7	40.9
Drinking ≤1 *go*/day	37.2	41.9	36.4	27.3
Drinking >1 *go*/day	38.4	31.4	40.9	31.8
BMI (kg/m^2)	23.7 ± 3.0	23.8 ± 2.9	25.5 ± 3.8	23.7 ± 2.9
Waist circumference (cm)	85.2 ± 8.5	85.9 ± 8.7	89.5 ± 14.6	84.4 ± 8.0
Total fat area (cm^2)	247 ± 101	253 ± 95	290 ± 120	240 ± 93
Visceral fat area (cm^2)	122 ± 56	124 ± 52	140 ± 42	115 ± 54
Subcutaneous fat area (cm^2)	125 ± 57	129 ± 55	150 ± 87	125 ± 52
Fasting glucose (mg/dl)	106 ± 20	108 ± 19	118 ± 39	109 ± 20
Fasting insulin (μU/dl)	6.7 ± 4.3	6.9 ± 4.1	9.2 ± 7.5	7.3 ± 4.4
HOMA-IR	1.79 ± 1.26	1.88 ± 1.27	2.71 ± 2.49	2.02 ± 1.36

Data are means ± SD unless stated otherwise.

fat mass was highly correlated with other measures of obesity (Pearson correlation coefficients: waist circumference 0.82, BMI 0.68, and subcutaneous fat mass 0.58), moderately with insulin (0.44), and weakly with fasting glucose (0.18).

As shown in Table 2, the odds of having colorectal cancer were increased in subjects with a higher visceral fat mass, with multivariable-adjusted ORs (95% CI) for the lowest through highest tertiles of 1 (reference), 2.17 (0.45–10.46), and 5.92 (1.22–28.65), respectively (P_{trend} = 0.02). Additional adjustment for BMI did not attenuate the association. In contrast, subcutaneous fat mass was materially unrelated to colorectal cancer prevalence, with a multivariable-adjusted OR for the highest versus lowest tertile of 1.08 (0.29–4.00). Higher levels of BMI or waist circumference were also associated with increased prevalence of colorectal cancer, with multivariable-adjusted ORs (95% CI; P_{trend}) for the highest versus lowest tertile of visceral fat area of 4.38 (0.82–23.25; 0.09) and 2.03 (0.57–7.25; >0.2) for BMI and waist circumference, respectively. With regard to colorectal adenoma, no association was seen with any measure of obesity, including visceral fat mass.

As shown in Table 3, the odds of colorectal cancer tended to increase with increasing fasting plasma glucose concentration and, to a lesser extent, with increasing fasting plasma insulin concentration and HOMA-IR. Multivariable ORs (95% CI; P_{trend}) for the highest versus lowest tertiles of glucose, insulin, and HOMA-IR were 4.40 (0.99–19.59; 0.04), 1.84 (0.47–7.15; >0.2), and 3.10 (0.71–13.54; 0.15), respectively. Additional adjustment for BMI attenuated the association with insulin and HOMA-IR but did not greatly change that with glucose. In contrast, no measurable association was seen between colorectal adenoma and any of the three blood measurements.

CONCLUSIONS— Among participants in a health screening program who underwent abdominal CT measurement, we found increased odds of early colorectal cancer in subjects with greater visceral fat mass, but not in those with greater subcutaneous fat mass. Markers of insulin resistance were also associated with a higher prevalence of colorectal cancer. In contrast, these associations were not observed for colorectal adenoma. To our knowledge, this study is the first to provide direct evidence of an association between visceral adiposity and colorectal cancer risk.

The present association between greater visceral fat area and increased prevalence of colorectal cancer is consistent with earlier epidemiological data showing a link between colorectal cancer and waist circumference or waist-to-hip ratio (4,5). In contrast, we observed no association with subcutaneous fat mass. This finding indicates that visceral but not subcutaneous adipose tissue disposition is involved in the promotion of colorectal carcinogenesis. Among studies that have measured visceral fat area using CT scanning in association with colorectal neoplasia (6–10), only one study (10) examined the association with colorectal cancer. Contrary to expectations, this study showed a higher prevalence of colorectal cancer in subjects with low rather than high visceral fat area. The authors speculated that this finding might have been due to weight loss induced by cancer progression. In our study, cancer in subjects included in the analysis was all screening-detected and early stage, and thus the results were unlikely to have been influenced by cancer-induced weight loss.

In contrast to the positive finding for colorectal cancer, we observed no association between any measure of obesity, including visceral fat area, and the prevalence of colorectal adenoma. Findings among studies that have measured abdominal fat area using CT are mixed: a significant positive association with visceral adiposity in a Japanese study (7) was subsequently both supported (9) and challenged (8,10). Further, in an ancillary study to the Polyp Prevention Trial (6), visceral fat area measured on CT was not associated with adenoma recurrence. The reason for this discrepancy among adenoma studies is not clear. Given that smoking is a strong determinant of both the prevalence of colorectal adenoma (18) and body weight (19), the null finding in our study might be attributable, at least in part, to the high proportion of subjects with a history of smoking (73%). The relation of obesity measures to colorectal adenoma might only be detected in populations with no or low-level exposure to smoking, as suggested by a positive finding among nonsmokers (7). Alternatively, if the major role of obesity in colorectal carcinogenesis is to enlarge existing adenomas, the present null finding may be ascribable to the small number of case subjects with large adenomas (≥10 mm: *n* = 15).

The insulin hypothesis has been proposed to explain the association between obesity or visceral adiposity and colorectal cancer (12,13). Prospective studies have shown an increased risk of colorectal cancer among individuals with higher

Table 2—*Associations of measures of obesity with the prevalence of adenoma and cancer in the colorectum*

	Colorectal adenoma				Colorectal cancer			
	1 (low)	2	3 (high)	P_{trend}	1 (low)	2	3 (high)	P_{trend}
n		86				22		
Total fat area (cm^2)*	<214	214–288	>288		<197	197–287	>287	
No. of case subjects/control subjects	33/85	22/86	31/87		4/21	8/22	10/23	
Crude OR (95% CI)†	1	0.63 (0.32–1.23)	0.87 (0.43–1.74)	>0.2	1	2.04 (0.52–7.96)	2.44 (0.63–9.44)	>0.2
Multivariable OR (95% CI)‡	1	0.64 (0.32–1.27)	0.87 (0.43–1.76)	>0.2	1	2.26 (0.52–9.82)	2.76 (0.64–11.87)	0.19
Visceral fat area (cm^2)*	<103	103–142	>142		<92	92–129	>129	
No. of case subjects/control subjects	29/85	27/86	30/87		3/21	6/22	13/23	
Crude OR (95% CI)†	1	0.90 (0.44–1.85)	1.02 (0.46–2.24)	>0.2	1	1.88 (0.42–8.35)	4.87 (1.11–21.42)	0.03
Multivariable OR (95% CI)‡	1	0.86 (0.41–1.78)	0.99 (0.45–2.20)	>0.2	1	2.17 (0.45–10.46)	5.92 (1.22–28.65)	0.02
Multivariable OR (95% CI)§	1	0.89 (0.41–1.97)	1.08 (0.42–2.81)	>0.2	1	2.09 (0.41–10.70)	8.42 (0.80–88.56)	0.08
Subcutaneous fat area (cm^2)*	<106	106–139	>139		<101	101–145	>145	
No. of case subjects/control subjects	30/85	31/86	25/87		7/21	7/22	8/23	
Crude OR (95% CI)†	1	1.0 (0.55–1.83)	0.78 (0.40–1.52)	>0.2	1	0.96 (0.26–3.46)	1.04 (0.30–3.66)	>0.2
Multivariable OR (95% CI)‡	1	1.01 (0.55–1.87)	0.82 (0.41–1.61)	>0.2	1	1.17 (0.30–4.51)	1.08 (0.29–4.00)	>0.2
Waist circumference (cm)*	<82	82–89	>89		<80	80–88	>88	
No. of case subjects/control subjects	24/83	32/87	30/88		6/21	4/22	12/23	
Crude OR (95% CI)†	1	1.28 (0.69–2.38)	1.22 (0.61–2.42)	>0.2	1	0.70 (0.18–2.78)	2.01 (0.58–6.95)	>0.2
Multivariable OR (95% CI)‡	1	1.37 (0.73–2.55)	1.18 (0.59–2.35)	>0.2	1	0.75 (0.18–3.13)	2.03 (0.57–7.25)	>0.2
BMI (kg/m^2)	<22.5	22.5–24.8	>24.8		<22.2	22.2–24.8	>24.8	
No. of case subjects/control subjects	29/84	29/85	28/89		3/20	8/23	11/23	
Crude OR (95% CI)†	1	0.98 (0.53–1.83)	0.89 (0.46–1.73)	>0.2	1	2.32 (0.56–9.68)	3.65 (0.81–16.44)	>0.2
Multivariable OR (95% CI)‡	1	0.99 (0.52–1.86)	0.90 (0.46–1.77)	>0.2	1	3.00 (0.61–14.86)	4.38 (0.82–23.25)	0.09

*Measured by abdominal CT at the umbilical level in supine position. †Crude. ‡Adjusted for smoking and alcohol drinking. §Additionally adjusted for BMI.

levels of postprandial insulin (4), C-peptide (20,21), a measure of average insulin secretion, and fasting glucose (4) at baseline, although the association with fasting insulin was less clear (4). In accordance with these data, we observed an increase, albeit without statistical significance, in the odds of colorectal cancer in subjects with higher levels of markers of insulin resistance, particularly fasting glucose. With regard to colorectal adenoma, although some studies have demonstrated an elevated risk among individuals with higher levels of fasting insulin (22) or fasting glucose (23), our data do not support a role of insulin resistance in the development of colorectal adenoma. Recently, Tabuchi et al. (24) reported similar findings in health checkup participants who underwent total colonoscopy: hyperglycemia was associated with an increased risk of colorectal cancer, but not with colorectal adenoma. Similarly, Chung et al. (25) demonstrated that glucose concentrations were more strongly associated with colorectal cancer than with adenoma. Further studies are required to determine whether insulin resistance and resulting conditions, including hyperinsulinemia and hyperglycemia, are more strongly involved in the development of cancer than in that of adenoma.

The present study has several methodological advantages over previous studies that directly measured visceral adiposity accumulation using CT. Control subjects were randomly selected from a population of screening participants, among whom the cases arose, and abdominal CT measurement was done before the diagnosis of colorectal neoplasia, precluding the possibility of bias in the selection of control subjects and assessment of exposure, both of which are major concerns in case-control studies.

Several limitations of the study also warrant mention. First, the number of case subjects with colorectal cancer was small (n = 22). Nevertheless, we were able to detect a statistically significant association with visceral fat area. Second, although the control subjects were selected from among examinees with a negative screening result, they were not confirmed to be polyp free and thus may have included patients with colorectal adenomas, leading to attenuation of the association. Given the low probability that the control series included subjects with undetected cancer, however, we believe that the present estimates for cancer were not subject to serious bias. Third, physical activity, a convincing protective factor for colorectal cancer (1), was not controlled for in the analysis; in any case, such control would not be methodologically valid if physical activity exerted an anticarcinogenic effect by decreasing visceral fat. An additional limitation was the lack of consideration of dietary factors. Finally, because the majority of study subjects were male employees working for a large-scale company in Japan, the results may not be generalizable to populations with different backgrounds.

In summary, the present study of screening participants who underwent abdominal CT scanning provides direct evidence for the hypothesis that visceral fat accumulation and insulin resistance promote carcinogenesis of the colorec-

Table 3—*Associations of glucose, insulin, and HOMA-IR with the prevalence of adenoma and cancer in the colorectum*

	Colorectal adenoma				Colorectal cancer			
	1 (low)	2	3 (high)	P_{trend}	1 (low)	2	3 (high)	P_{trend}
n		86				22		
Fasting glucose (mg/dl)	<100	100–108	>108		<99	99–108	>108	
No. of case subjects/control subjects	32/74	24/93	30/91		4/21	6/22	12/23	
Crude OR (95% CI)*	1	0.57 (0.30–1.08)	0.73 (0.39–1.36)	>0.2	1	1.69 (0.36–7.96)	3.12 (0.76–12.74)	0.09
Multivariable OR (95% CI)†	1	0.62 (0.32–1.19)	0.76 (0.40–1.42)	>0.2	1	1.76 (0.35–8.69)	4.40 (0.99–19.59)	0.04
Multivariable OR (95% CI)‡	1	0.62 (0.32–1.20)	0.76 (0.41–1.44)	>0.2	1	2.17 (0.41–11.50)	4.07 (0.86–19.37)	0.07
Fasting insulin (μU/dl)	<4.7	4.7–7.4	>7.4		<5	5–7.8	>7.8	
No. of case subjects/control subjects	29/85	29/83	28/90		5/21	8/22	8/23	
Crude OR (95% CI)*	1	1.02 (0.57–1.85)	0.91 (0.50–1.66)	>0.2	1	1.55 (0.45–5.32)	1.38 (0.40–4.76)	>0.2
Multivariable OR (95% CI)†	1	1.14 (0.61–2.12)	1.08 (0.58–2.03)	>0.2	1	1.65 (0.38–7.28)	1.84 (0.47–7.15)	>0.2
Multivariable OR (95% CI)‡	1	1.15 (0.62–2.15)	1.15 (0.57–2.31)	>0.2	1	1.88 (0.39–9.03)	1.29 (0.28–5.84)	>0.2
HOMA-IR	<1.2	1.2–2.05	>2.05		1.33	1.33–2.04	>2.04	
No. of case subjects/control subjects	31/85	30/86	25/87		4/21	8/22	9/23	
Crude OR (95% CI)*	1	0.95 (0.53–1.72)	0.79 (0.43–1.45)	>0.2	1	1.85 (0.52–6.62)	1.89 (0.51–6.94)	>0.2
Multivariable OR (95% CI)†	1	1.08 (0.58–2.00)	0.89 (0.47–1.68)	>0.2	1	2.60 (0.62–10.97)	3.10 (0.71–13.54)	0.15
Multivariable OR (95% CI)‡	1	1.08 (0.58–2.03)	0.91 (0.45–1.83)	>0.2	1	2.63 (0.60–11.41)	2.20 (0.45–10.81)	>0.2

*Crude. †Adjusted for smoking and alcohol drinking. ‡Additionally adjusted for BMI.

tum. Because adipose tissue secretes various hormones that may play a role in the development and progression of cancer not only through their effect on insulin resistance but also by directly controlling cell proliferation, the biological mechanisms linking visceral fat disposition to cancer risk should be further explored.

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Relations Between Waist Circumference at Four Sites and Metabolic Risk Factors

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The location of waist circumference (WC) measurement differs among diagnostic guidelines for the metabolic syndrome. The present study examined which of four WC measurements was associated most strongly with the clustering of metabolic risk factors in cross-sectional study. The subjects comprised 1,140 Japanese employees, aged 20–70 years, who underwent health examinations in 2007 and 2008. WC was measured at (i) the narrowest part of the waist, (ii) midway between the lowest rib and the iliac crest, (iii) the umbilical level, and (iv) immediately above the iliac crest. A receiver operator characteristic (ROC) curve was used to assess the ability of each WC measurement to predict the presence of two or more other components of the metabolic syndrome, as defined by the National Cholesterol Education Program's Adult Treatment Panel III (NCEP-ATP III) in 2005. Multiple risk factors were seen in 43.0% of the men and 12.9% of the women. The minimum and maximum WC measurements differed by 3.9 cm among the men and 12.6 cm among the women. The areas under the curve examining the ability of the four WC measurements to predict the clustering of multiple risk factors were similar. If the same WC cutoff value was applied, the prevalence of the metabolic syndrome changed considerably according to the site of WC measurement. The four WC measurements had similar screening abilities. Given the differences in the WC values according to the site of measurement, WC must be measured at the site specified by each diagnostic guideline.

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INTRODUCTION

The metabolic syndrome is characterized by central obesity, impaired glucose tolerance, high blood pressure, and abnormal lipid metabolism (1), and is related to an increased risk of cardiovascular disease (2). The prevalence of the metabolic syndrome has been increasing worldwide, in parallel with the increasing prevalence of obesity (3), and an urgent need for preventive strategies exists.

BMI is used as a measure of overall obesity, but central obesity is increasingly recognized as a more important risk factor for hypertension, coronary heart disease, and type 2 diabetes (4). Visceral fat area, which is best measured using computed tomography, is reportedly more reliable for identifying components of the metabolic syndrome (5), but waist circumference (WC) is used as a measure of central obesity for practical reasons. So far, 14 different sites have been proposed for the measurement of WC; however, a universal standard for measuring WC does not yet exist (6). Among the diagnostic criteria for the metabolic syndrome, at least three different locations are used for WC measurements (1,7–9). Which WC measurement location best predicts the clustering of metabolic risk factors and related diseases remains uncertain.

In the present study, conducted in a population of Japanese workers, we measured WC at (i) the narrowest part of the waist, as recommended in the Anthropometric Standardization Reference Manual (10); (ii) midway between the lowest rib and the iliac crest, as defined by the WHO (World Health Organization) (7) and the IDF (International Diabetes Federation) (8); (iii) the umbilical level, as defined in the Japanese metabolic syndrome guidelines (1); and (iv) immediately above the iliac crest, as defined in the National Cholesterol Education Program's Adult Treatment Panel III (NCEP-ATP III) guidelines (9) in 2005. Then, we compared the abilities of these WC measurements to detect the clustering of metabolic risk factors to determine which WC measurement is most suitable for diagnosing the metabolic syndrome.

METHODS AND PROCEDURES

In 2007 and 2008, all 2,431 employees who underwent a routine health examination at the Koukankai Tsurumi Occupational Health Center, Kanagawa, Japan were invited to participate in the present study; 1,745 (71.8%) employees agreed and gave their consent. However, 605 employees who had not fasted for ≥6 h after their last meal were excluded. Thus, 1,140 subjects (969 men and 171 women) were included in the present analysis. The present study

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was approved by the Ethics Committee of the International Medical Center of Japan, and written informed consent was obtained from all the subjects.

A self-administered questionnaire that included questions regarding medical management, including both medications and lifestyle modification, for hyperlipidemia, hypertension, and diabetes was given to each participant at the time of the health examination. Body height and weight were measured using an automated scale (AD-6225A; A&D, Tokyo, Japan), and the BMI was calculated as the weight/height^2 (kg/m^2). Measurements were obtained with the subjects in a standing position, both arms free at their sides, breathing naturally. WCs were directly measured with fiberglass tape placed on the skin: the narrowest part of the waist (WC1), midway between the lowest rib and the iliac crest (WC2), the umbilical level (WC3), and immediately above the iliac crest (WC4) (7). Prior to the survey, a training session on WC measurements was held to reduce measurement biases. Each WC site was measured once by trained researchers and laboratory technicians. Blood drawing was conducted by a registered nurse at Koukankai Tsurumi Occupational Health Center, and measurements were conducted at Tsurumi Koukan Hospital. Blood pressure was measured using an automated sphygmomanometer (TM-2655P; A&D) after the subjects had rested for 15 min. The serum concentrations of fasting glucose, triglycerides, and high-density lipoprotein-cholesterol were measured using the HK enzyme method, the GK enzyme method, and a direct method, respectively. The coefficient of variations (%) of fasting glucose, triglycerides, and high-density lipoprotein-cholesterol were 0.56, 1.68, and 2.0%, respectively.

Definition of risk-factor clustering

According to the NCEP-ATP III diagnostic criteria for the metabolic syndrome in 2005 (9), we defined subjects with two or more of the following factors as having a cluster of metabolic risk factors: (i) triglycerides ≥150 mg/dl (1.69 mmol/l), (ii) high-density lipoprotein-cholesterol <40 mg/dl (1.03 mmol/l) in men and <50 mg/dl (1.29 mmol/l) in women, (iii) systolic blood pressure ≥130 mm Hg or diastolic blood pressure ≥85 mm Hg, and (iv) fasting plasma glucose ≥100 mg/dl (5.51 mmol/l). Subjects receiving treatment for hyperlipidemia, hypertension, or diabetes were deemed as having the respective risk factors, regardless of their health checkup data.

Statistical analyses

All the analyses were performed according to sex. We tested the difference between WC1 and other WCs using Dunnett's test after two-way analysis of variance, where the two factors were measurement sites and individuals. We calculated the Pearson's correlation coefficients for the five anthropometric measurements (four WCs and BMI). To establish equations for converting one WC to another, linear regression analyses were used to obtain the regression coefficients and intercepts (see **Supplementary Table S1**). We conducted a stratified analyses by BMI (<25, ≥25) and age (<55 years and ≥55 years). The stratified analyses were conducted only in men, due to the small sample size of women. However, the results of the analyses were similar; thus, we presented only the results for all subjects. We also drew the receiver operator characteristic (ROC) curves for each WC in association with the presence of two or more risk factors of the metabolic syndrome and calculated the corresponding area under the curve (AUC). Test for the equality of the AUC, using an algorithm suggested by DeLong, DeLong, and Clarke-Pearson, was conducted among four WCs, and four WCs plus BMI (11). The pairwise comparisons of BMI with four WCs were also done, where P values for multiple tests (four comparisons) were adjusted by Bonferroni–Holm's method. Furthermore, the cutoff value yielding an 80% sensitivity, together with the corresponding specificity, for the prediction of clusters of metabolic risk factors was calculated for each WC. A P value <0.05 was considered statistically significant. All analyses were performed using SPSS for Windows, version 15.0 (SPSS, Chicago, IL) and Stata 10 (StataCorp, College Station, TX).

RESULTS

The mean (s.d.) age of the study subjects was 52.9 (9.0) years for the men and 47.0 (9.8) years for the women. The characteristics of the subjects are shown in **Table 1**. The mean (s.d.) BMI was 24.1 (3.1) kg/m^2 for the men and 21.8 (3.0) kg/m^2 for the women. The BMI range was from 14.9 to 39.4 kg/m^2. Clusters of two or more risk factors were seen in 43.0% of the men and 12.9% of the women.

Table 2 shows the results of the WC measurements at the four sites. The WC values increased in the order of WC1, WC2, WC3, and WC4 for both sexes; the respective means were 83.3, 85.2, 86.8, and 87.2 cm in men and 69.6, 73.1, 78.8, and 82.5 cm in women. The mean difference between the minimum (WC1) and the maximum (WC4) values was much greater in women (12.6 cm) than in men (3.9 cm).

Table 3 shows the correlations among the four WC measurements and BMI. The WC measurements were strongly correlated (r >0.9) in both men and women. Each WC was also strongly correlated with the BMI in both men and women (r >0.8).

An ROC analysis was performed to determine which WC best predicted clusters of multiple risk factors. The ROC curves

Table 1 Characteristics of study subjects

	Men (n = 969)	Women (n = 171)
Age (years)[a]	52.9 (9.0)	47.0 (9.8)
Body height (cm)[a]	169.0 (6.1)	156.3 (5.9)
Body weight (kg)[a]	68.9 (10.3)	53.3 (8.2)
BMI (kg/m^2)[a]	24.1 (3.1)	21.8 (3.0)
High serum triglycerides (%)	33.8	8.8
Low serum HDL-cholesterol (%)	12.8	7.0
High blood pressure (%)	52.0	25.7
Impaired fasting glucose (%)	40.2	12.9
Multiple risk factors (%)	43.0	12.9
Current smoking (%)	36.1	7.1

High serum triglyceridβs: , 150 mg/dl (1.69 mmol/l). Low serum HDL-cholesterol: <40 mg/dl (1.03 mmol/l) for men and <50 mg/dl for women (1.29 mmol/l). High blood pressure: systolic blood pressure ≥130 mm Hg or diastolic blood pressure ≥85 mm Hg. Impaired fasting glucose: ≥100 mg/dl (5.51 mmol/l). Multiple risk factors: having two or more risk factors of metabolic syndrome defined by NCEP-ATP III (2005).
HDL, high-density lipoprotein; NCEP-ATP III, National Cholesterol Education Program's Adult Treatment Panel III.
[a]Values are mean (s.d.).

Table 2 Comparisons among waist circumference measurements at different sites

Measurement site	Men (n = 969)	Women (n = 179)
WC1	83.3 (7.8)	69.9 (7.8)
WC2	85.2 (8.3)*	73.1 (8.5)
WC3	86.8 (8.0)*	78.8 (8.9)
WC4	87.2 (7.8)*	82.5 (8.6)

Values are mean (s.d.) (cm).
WC1, narrowest part of waist; WC2, midway between the lowest rib and the iliac crest; WC3, umbilical level; WC4, immediately above the iliac crest.
*P value <0.05 (compared with WC1).

Table 3 Correlation between waist circumference measurements at each site and BMI

	Men				Women			
	WC2	WC3	WC4	BMI	WC2	WC3	WC4	BMI
WC1	0.980	0.960	0.937	0.903	0.958	0.922	0.912	0.923
WC2		0.977	0.954	0.896		0.943	0.930	0.899
WC3			0.979	0.887			0.936	0.894
WC4				0.871				0.873

Values are the Pearson's correlation coefficients.
WC1, narrowest part of waist; WC2, midway between the lowest rib and the iliac crest; WC3, umbilical level; WC4, immediately above the iliac crest.

Table 4 Areas under the curve of receiver operator characteristic for diagnosing two or more metabolic syndrome risk factors for each waist measurement site and BMI

	Area under the curve				Asian WC cutoff	
Measurement site	Mean	s.e.	WC or BMI corresponding to 80% sensitivity	Specificity corresponding to 80% sensitivity (%)	Sensitivity of multiple risk factors (%)	Specificity of multiple risk factors (%)
Men						
WC1	0.668*	0.017	79.7 cm	43.8	27.1	86.8
WC2	0.671*	0.017	81.3 cm	44.4	35.7	81.7
WC3	0.660	0.017	83.0 cm	42.0	41.0	77.0
WC4	0.657	0.018	83.6 cm	41.5	43.9	76.3
BMI	0.639	0.018	22.6 kg/m^2	42.6	—	—
Women						
WC1	0.780	0.058	69.7 cm	61.1	50.0	95.3
WC2	0.780	0.056	71.9 cm	57.0	59.1	83.9
WC3	0.772	0.057	78.1 cm	55.0	72.7	65.1
WC4	0.748	0.065	81.1 cm	51.7	86.4	46.3
BMI	0.779	0.060	21.6 kg/m^2	61.7	—	—

Asian WC cutoff: 90 cm for men and 80 cm for women. Multiple risk factors: having two or more risk factors of metabolic syndrome defined by NCEP-ATP III (2005).
NCEP-ATP III, National Cholesterol Education Program's Adult Treatment Panel III; WC1, narrowest part of waist; WC2, midway between the lowest rib and the iliac crest; WC3, umbilical level; WC4, immediately above the iliac crest.
*P value <0.05 (BMI vs. each WC).

for the four WC measurements were similar (data not shown). Table 4 shows the AUC values for the four WC measurements and the BMI. In general, the AUC values were greater in women than in men. The WC measurement with the largest AUC value was WC2 for men, and WC1 and WC2 for women. However, the AUC values for the four WC measurements were not significantly different among either men or women. The respective cutoff levels yielding an 80% sensitivity for the prediction of clusters of multiple risk factors for WC1, WC2, WC3, and WC4 were 79.7, 81.3, 83.0, and 83.6 cm in men and 69.7, 71.9, 78.1, and 81.1 cm in women.

DISCUSSION

In a population of Japanese workers, we measured WC at four sites and assessed the relations of these measurements to metabolic risk factors. We identified a significant difference in WC according to the site of measurement, especially in women, although the four WC measurements were each strongly correlated with metabolic risk factors in both men and women. In an ROC analysis for the prediction of clusters of metabolic risk factors, the AUC values did not differ significantly among the four WC measurements.

Some previous studies have also examined differences in WC measurements according to the site of measurement. Wang *et al.* (12) reported that, in a population consisting of several ethnicities, the mean difference between the narrowest part of the waist (WC1) and midway between the lowest rib and the iliac crest (WC2) was 1.6 cm in men (n = 49) and 2.7 cm in women (n = 62). In a Danish study of 416 middle-aged subjects (13), the mean difference between WC1 and measurements at the umbilical level (WC3) was 0.7 cm for men and 5.0 cm for women. Willis *et al.* (14) reported that in 266 overweight and obese white men and women, the mean difference between WC1 and WC3 was 4.6 cm for men and 10.0 cm for women. Mason and Katzmarzyk (15,16) reported that in about 500 men and women, the mean difference between WC1 and WC3 was 2.5–2.6 cm for men and 8.6 cm for women. In the present study of Japanese workers, the difference between WC1 and WC2 was 1.6 cm in men and 2.2 cm in women and that between WC1 and WC3 was 3.3 cm in men and 8.4 cm in women.