1986年、WHOが「人間は誰でもがんの痛みから逃れる権利を持つ」という宣言のもと、世界中どこでも、医師なら誰でもできる、痛みをとる方法を提唱したときからです。これがWHO方式と呼ばれる、医療用麻薬を使う画期的な方法でした。

このWHO方式は、痛みの程度に応じて、三段階にクスリを使い分けることになっています。まず、軽い痛みには非ステロイド性消炎鎮痛剤（非オピオイド鎮痛薬・註1）。それでは対処できない中程度の痛みには、弱オピオイドに分類される薬剤を使う。それでもとれない痛みには、強オピオイドを使う、というもので、このオピオイド鎮痛薬［註2］がモルヒネなどを中心とした医療用麻薬です。

大切なことは、こういったクスリを「痛みをとるために」使うことです。つまり、鎮痛効果が途切れないように、一定の間隔で飲んでいただきますから、患者さんには、つかうクスリや、飲む意味などを正確に説明して、納得していただくことが重要です。

とくに日本では、まだモルヒネへの偏見と誤解が、患者さんはもちろん、医師のあいだにも残っています。

ですから、私はクスリを出す前、口を酸っぱくして、痛みで服用しているかぎり、麻薬中毒にはならないし、廃人にもならない、頭がおかしくもならないし、命を縮めたりもしないということをお話しし、「できるだけ時間を決めて飲んでください」とお願いするのです。

もう一つ、お願いすることがあります。「いまのあなたの状態を正直に話してください」ということです。

私たちも患者さんをよく観察して、痛みのサインなどを見逃さないように努力していますが、痛みの程度は患者さん本人しかわかりません。

いまどの程度痛むのか、新しいクスリをのんだあと、痛みの強さはどう変わったのか、変化がないのか、少しは軽くなったのか、また、ほかの症状は出なかったのか……。

もしクスリが効いていないのなら、別のクスリに替えたり、量を増やさなくてはなりません。起こることがわかっている副作用については、それを抑えるクスリもいっしょに飲んでいただきますが、効き方は人によって違います。その決め手は、患者さんご本人の言葉だけです。

痛いことを痛いというのは泣き言ではありません。痛みや苦しみは取り除くべきものですし、緩和ケアで出しているほとんどのクスリは、効けば、痛みがなくなることが実感できます。「気のせいか、少しは楽になった」という程度ではありませんから、正直に痛みの状況（いつから、どこが、どのように痛むのか）などを教えていただきたいのです。

痛みやつらさを口で言うのがイヤなら、日記とかメモのかたちでもけっこうです。よく病院では、痛みのスケールを出しています。1センチ刻みの目盛りがついていて、痛みの具合を記したり、さまざまな表情をしている顔に丸をつけたり……あれは、患者さんが感じている痛みの強さを共有しようという試みなのです。

副作用をケアしながらクスリを飲む

どういうふうに痛みをとるのか、具体的にお話ししましょう。

痛みの80〜90パーセントは、モルヒネを中心とする飲み薬で調節できます。いつも一定濃度を保つのがコツですから、決まった時間にのんで、痛みが出ないようにするのですが、痛みの強さが一人一人違うように、効果も人によって違います。ですか

［註1］非オピオイド鎮痛薬●痛みが弱いときに使われる医療用麻薬以外の鎮痛薬です。よく使われるのがエヌセイド（非ステロイド性消炎鎮痛剤）のアスピリンやイブプロフェンか、アセトアミノフェンで、頭痛や腰痛、歯の痛みなどにも使われる、おなじみのクスリです。

［註］オピオイド鎮痛薬●法律で医療用に許可されている麻薬です。ニュースなどで報道されている乱用麻薬とは別のもので、麻薬中毒や依存症にはなりません。効果によって弱と強があり、強オピオイド鎮痛薬のなかで、がんの痛みにもっとも威力を発揮するのがモルヒネで、そのほか新しいタイプのクスリとして、フェンタニルやオキシコドンも使われるようになっています。

なおオピオイドとは、痛みを脳に伝える神経にあるオピオイド受容体に結合する物質で、結合した受容体からは痛みの信号が脳に伝わらないことで、鎮痛作用が出るものです。

*がん疼痛治療を受けている患者さんのアンケート（がん疼痛治療患者調査レポートより改変）

❶基本的にがんの痛みは我慢するものだと思いますか（総数3百人）

非常にそう思う　34・0％
やや、そう思う　24・3
どちらともいえない　24・0
あまりそう思わない　14・7
全くそう思わない　3.0

❷がんの痛みについて、あなたが最初に支障を感じたものを一つだけお教えください（総数4百人）

気分・情緒　34・8％
睡眠　17・3
運動　10・5
基本的な生活習慣　10・3
仕事や家事　8.8
日々の生活を楽しむこと　8.5
食欲　8.0
歩くこと　2.0

❸医療用麻薬（オピオイド）の使用を避けたいと思う理由をお教えください（総数41人の複数回答）

中毒や依存症になると思うから　95・1％
痛みを抑える最後の手段という気がするから　95・1
寿命が縮むと感じるから　61・0
次々と服用する量が増やされるのがいやだから　39・0
副作用が強いから　24・4
使用しても痛みが収まらないことがあるから　9.8

ら、最低用量から痛みがとれるまで増量して、その患者さんに最適な量を見つけます。この間、2～3日はかかるでしょう。

ふだんはMSコンチンというモルヒネの徐放剤（効き目が長く続くクスリ）をのんでもらい、ときどき急に激しく痛むときのために、飲んで10分くらいで効果が出る頓服（レスキュードーズ）も処方しておいて、痛いときにいつでも追加ができるという体制で臨みます。

問題は、モルヒネの副作用です。服用直後から吐き気・嘔吐がでますし、便秘はほぼ必発です。眠気も初めのころには出ることがあり、モルヒネをうまく使うためには、この副作用対策を確実に行なわなくてはなりません。

嘔吐・吐き気には制吐剤を、便秘には緩下剤を処方します。それでも吐き気や便秘が調節できないときには、オキシコドンやフェンタニルという、モルヒネよりも鎮痛効果が高く、しかも副作用が多少少ないという新しいタイプのクスリに変えることもあります。

たとえば、オキシコドンはモルヒネの1.5倍の鎮痛効果がありますし、貼り薬のフェンタニルは、100倍の鎮痛効果があるといわれていて、一度貼れば三日間効果が持続し、副作用も少ないクスリです。ただ、それぞれよい点、わるい点があるので、専門家に相談して使用します。

注意しなくてはいけないのは、こんなクスリを総動員しても、なかなかとれない痛みがあるということです。その代表が、神経が障害されたときに起こる神経因性疼痛といわれる頑固な痛みでしょう。

肺がんで、がんが胸壁のほうに浸潤して肋間神経を巻き込むと、神経因性疼痛が起こるし、肺尖部にできたがんが上のほうに広がり、腕のつけ根にある腕神経叢という神経のかたまりをまきこむと、激しい痛みとしびれを患者さんにもたらします。このような痛みは、乳がんでも大腸がんや子宮がん、膵がんでも起こります。

あるいは、がんが脊椎や大腿骨に転移すると、簡単に骨折するようになって、別の激しい痛みを起こします。これらの痛みは、オピオイド系の鎮痛薬だけでは対応し切れません。

こういう痛みにどう効果的に対処できるかで、緩和ケア医の力量が判断できます。そのために私たち麻酔科の経験は重要ですし、チームに放射線療法の医師や理学療法士が参加している意味も出てくるのです。

神経因性疼痛には国立がんセンター方式で

この神経因性疼痛の特徴は、さわっても感覚がないところがどうして痛いのだろうとか、逆に少し触れただけで、どうしてこんなに飛び上がるように痛むのかと、患者さんご自身でなかなか理解できないことですから、いっそう不安になりがちです。

そういう患者さんに、私たちはまず鎮痛補助剤といわれているクスリを使います。抗てんかん剤や抗うつ剤、抗不整脈剤を、WHO方式にならって、段階的に増していきます。

第一段階として抗痙攣薬のランドセンを使う。一日経って効果がないときには抗うつ薬のアモキサンを使う、それでもだめならメキシレチンを使用する……この方式は現在、「国立がんセンター方式」として、一部に広まっています。

次に使うのが、麻酔科の専売特許である神経ブロックです。痛みを伝える神経に薬剤を注入して痛みが伝わらないようにする方法で、膵がん

●日本ホスピス緩和ケア協会　http://www.hpcj.org
●在宅ケアデータベース　http://www.homehospice.jp/db/db.php
●日本ホスピス・在宅ケア協会　http://www.hospice.jp/
●在宅ケアを支える診療所・市民ネットワーク　http://www.home-care.ne.jp/

のときの背中の痛みには腹腔神経叢ブロックを行ないますし、直腸がんが仙骨神経を侵したときの激しい痛みには、くも膜下フェノールグリセリンブロックを行ないます。

がんが骨に転移したときの痛みには、放射線の照射が効果的ですが、脊椎や腰椎に転移して骨が弱り、ぐらぐら動いて痛いときには、それを支える骨セメント注入法が効果的な場合がありますし、がんが転移して脊椎や大腿骨が骨折したときには、脊髄の硬膜外ブロックも効果的です。

床ずれにも硬膜外ブロックを使うことがあります。褥瘡を起こす患者さんは栄養状態がわるく、その部分は血流も悪くなっていますから、まず痛みをとって、その部分を洗浄し、治療をしていくことになります。

化学療法中になった口内炎には、イギリスなどではモルヒネで口をゆすぐ製品が発売されていて、モルヒネの新しい使い方として注目されています。重症の口内炎や腸炎の痛みには、PCAポンプといって、患者さん自身が痛いときにボタンを押せば、モルヒネなどの薬剤が血液に入るというポンプがあります。コンピュータで制御されていて、安全に行なわれます。

息苦しさをとるのも、少量のモルヒネを中心として、抗不安薬、ステロイド、気管支拡張薬を組み合わせて使うことがよいとされています。息苦しさは、患者さんがもっとも精神的にも身体的にも苦痛を味わう症状で、酸素が足りないのかと、よく酸素吸入をされますが、実は、人間のからだにある息苦しさを伝えるシステムによるものですから、酸素より、モルヒネのほうが有効なこともあるのです。

また、ステロイドというクスリは、だるさ、何をする気にもならないという全身倦怠感をとるのにも使われます。

というわけで、がんの患者さんが悩んだり苦しんだりするさまざまな症状の大部分は、私たち緩和ケアで充分フォローできます。不安が痛みを増幅させ、困難感を増す。それがさらに不安をつのらせるという悪循環を断ち切るのが、私たちの仕事なのです。

患者さんに優しく親切に

いま国の政策として、緩和ケア医をふやそうとしています。WHO方式がありますから、マニュアルの部分は、意外に短期間で学べます。

しかし、それで一人前ではありません。WHO方式が全員にあてはまるわけではないし、モルヒネが効きにくい痛みにも、数多くぶつかります。しかも、緩和ケア医は、チームのリーダーになって、他の職種の人たちとやっていかなければいけません。そういうことを考えると、一生修行するつもりでがんばっています。

その際もっとも大事なことは、患者さんに親切に接するという資質です。患者さんに優しい気持ちがなければ、緩和ケアはうまくいきません。

実際の診療では、マニュアルどおりにはいきません。思い通りにならないこともたくさん出てきます。私も、本当に困っている人の役にたてたのだろうかと、いつも心残りを抱えながら、次の患者さんに会うときには改善していこうと考えています。それはこれからも続くことでしょう。

なお、ここまでお話ししてきた緩和ケアチームは、病院の中で活動し、治療していくグループです。緩和医療には、ほかに緩和ケア病棟と在宅ケアがありますが、患者さんに接するスタンスは変わりません。詳しくは、それぞれの協会にお尋ね下さい。

Ⅱ．緩和ケアにおけるコンサルテーション活動の専門性

2．緩和ケアチームで活動する医師の役割と実際―1）緩和ケア担当医の立場から

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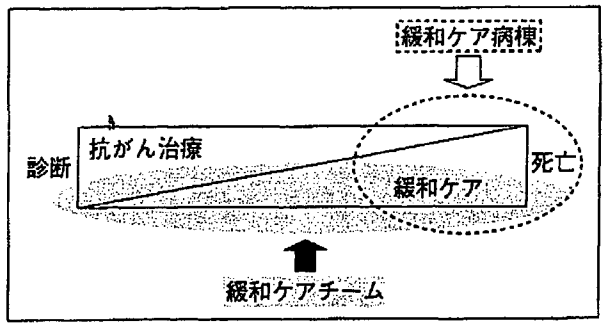
緩和ケアチームの緩和ケア医に求められる役割

緩和ケアチームの役割とは，一般病棟における緩和ケアの普及である[1,2]が，この緩和ケアの概念は近年の発展に伴い大きく変化してきた。この変遷とともに緩和ケアチームの緩和ケア医は，これまでの緩和ケア病棟でのそれとは異なる役割を担うようになっている。

まず，緩和ケア病棟では保険診療の制約からいわゆる終末期患者のみが対象となるのに対して，チームでは抗がん治療中の患者にも関わることが可能である点が挙げられる（図1）[3]。WHO（世界保健機関）による緩和ケアの定義も近年大きく変化したように，緩和ケアとは決してがん終末期に限定されるべき概念ではない。抗がん治療と緩和ケアは決して相反する概念ではなく，お互い相補的なものである。よって，緩和ケアが抗がん治療に並行して提供されることによってはじめて医療の本質である「全人的ながん診療」となりうる。そのことから，緩和ケア病棟における終末期患者に限った緩和ケアを「狭義の緩和ケア」と呼ぶならば，チームにはWHOが提唱する抗がん治療中から並行して行われる緩和ケア，すなわちがん診療全体をカバーする「広義の緩和ケア」（図1）が求められているといえる。

チームの緩和ケア医がこれを実現させるためには，がん診療の流れの中で患者と関わっていくことがなによりも重要であり，そのためには主治医との綿密なコミュニケーションが欠かせない。

2点目として，緩和ケア病棟の緩和ケア医は患者にとって主治医であるのに対し，チームの緩和ケア医の場合は基本的に主治医をサポートするコンサルテーション医であるという点である。これまでの状況を考えると，チームの緩和ケア医が緩和ケア病棟と同様に個々の患者に対して主治医として関わることはもちろん必要な場合もあるだろうが，このやり方だけでは病院全体を対象とする緩和ケアチームの場合には限られた時間の中での限界が生じてくる。また，不必要に関わりすぎてしまうことによって，実際の主治医とチームの間でケアに対する責任所在が不明確となる危険性や，主治医がチームに頼り患者から離れてしまう結果，長期的にみると一般病棟での緩和ケアの能力が逆に低下する危険性がすでに指摘されている[4~8]。



■図1　がん診療における緩和ケアチームの役割の模式図

緩和ケアチームが少しでも多くのがん患者が緩和ケアの恩恵を享受できるようになることを目指して造られたことからすると，チームの緩和ケア医にはコンサルテーション医として医療者への教育を意識した関わり方が重要となる[4, 9, 10]。特に，チームの新設で期待されたのは，一般病棟における終末期がん患者に対するがん性疼痛治療の遅れを取り戻すことであり，すなわち，まずは世界の標準治療である「WHO 方式に基づくがん性疼痛治療」を一般病棟において普及させる活動スタイルがチームの緩和ケア医には求められている。

3点目には，これまで述べてきたチーム外での役割のほか，緩和ケアチームの緩和ケア医はチーム内における役割についても理解しておくことが重要である。なぜなら，これまでの多くの緩和ケアチームにおける困難な状況が物語っているように[3, 11]，異なる性格，異なる背景を持つメンバーがそれぞれ異なる役割を担ってひとつのチームとして効果的に機能していくことは決して容易ではないためである。さまざまな職種が集まったグループにはチームダイナミクス（team dynamics）が働き，必然的にさまざまな障害（conflict）が生じてくる[4, 12]。これらの障害に対処していくためにはチーム内での連携（co-ordination）が求められており，その実現には効果的なコミュニケーションとリーダーシップが必要とされる。

すなわちチームの機能の円滑化に向けて緩和ケアチームの医師は，このような多職種からなるチームにおいては必然的にさまざまな障害が発生すること，そしてそれをいかに避けるかではなく，どのようにさらなるチーム力の向上につなげられるかを学び，チームの一員としていかにチームを効果的に機能させることに貢献できるかを知っておく責任がある。また，これらの障害に対処していく過程でチームには人のライフサイクルのような発達段階が生じるとされ，チームの発展の過程として自分たちがどの段階にいるのか客観的に知っておくことが，いざ困難に実際に遭遇した際に役立つものと思われる[12]。

緩和ケアチームの緩和ケア医の実際の診療手順

緩和ケアチームの緩和ケア医の関わり方にはいまだゴールドスタンダードと呼べるものはなく，それぞれの施設で，そのチームが期待されている役割を主治医との話し合いなどを通じてひとつ一つ見極めて，真の目標である「緩和ケアの普及」に向けてさまざまなニーズにすこしでも応えていくことが必要と考えている。ここでは，当院での現状を例として，チームの緩和ケア医に依頼があった場合についてその具体的な活動の流れを以下に示す[13]。

1）まず，緩和ケアチームの活動は原則として主治医が直接チームに依頼することから始まる。これは基本的に患者の全責任はその主治医にあるためである。また，依頼の際，主治医には具体的な依頼内容を他科依頼票もしくはカルテ記載で示してもらうようにしている。主治医が緩和ケアチームに依頼するきっかけ（これを「主治医のニーズ」と呼ぶ〈表1〉）はさまざまであり，このような主治医のニーズに対して当院では緩和ケア医と精神科医，看護師がそれぞれ別々に窓口を設け，緩和ケアチーム全体への依頼という形ではなく，どの職種へも直接依頼できるようにしている。

たとえば，がん性疼痛マネジメントに関する依頼の場合には，身体症状マネジメントを専門とする緩和ケア医が窓口となり，チームの中心となって対応するというものである。これにより，チーム全体でひとつの窓口で依頼を受けるよりも主治医のニーズがより明確化され，多岐にわたるニーズにより迅速に対応でき，またチーム全体として

■表1　緩和ケアコンサルテーションにおける主治医のニーズ（依頼内容）

- 身体症状マネジメント
- 精神症状マネジメント
- 終末期における患者の自己決定のサポート
- 患者の終末期における体制づくり
- 予後の判断
- 退院に向けたプランニングサポート

はより多くのニーズに応えることができるという利点につながっているものと考えている。

2) 次に，その依頼された内容の「難易度」を判断する。たとえば，オピオイドが効きやすい痛みに対して鎮痛薬の処方からすべてお任せしますという依頼と，オピオイドが効きにくい難しい痛みなのでいろいろ工夫してみたがうまくいかずに困っているという依頼とを比較すると，明らかに疼痛治療における難易度は異なるといえる。

これを当院で用いている「難易度」表（表2）で表現すると，前者はprimaryレベルで，後者はsecondaryレベル以上に相当する。神経ブロックのような専門的技術・管理を要する難治性疼痛や，新薬の臨床試験への参加を必要とする場合などに関してはtertiaryレベルに相当すると考えている。

ただ，これらの判断は緩和ケアに関する教育カリキュラムが医学教育や臨床研修を通じて確立していないこともあり，その依頼した医師や患者の状態，その対応に必要な治療法のエビデンスレベル，またそれぞれの施設の状況などに応じて変化するものであって構わないと考えている。

3) 緩和ケアコンサルテーションの内容と難易度を考慮しながらチームとしてどのように関わるかをカンファレンスにて相談したのちに，主治医と相談して最終的な方針を決定する。そして緩和ケア実施計画書に緩和計画を具体的に記載し，緩和ケア実施計画書を患者に示して署名にて同意を得る。主治医のニーズに対してコンサルテーション医としてどのように関わるか（表3）については，主治医のニーズや介入内容の難しさ，チームのキャパシティーなどを考慮している。それとともに限られた時間の中で主治医のニーズにできるかぎり応えながら，より多くの患者の症状緩和に努め，さらには病院全体の緩和ケア向上につながるような関わり方を心がけている[14]。

4) 翌日以降は，依頼患者を「関わり方のレベル」に応じて回診し，緩和ケア医としての意見・方針を患者や主治医，病棟看護師へ適宜フィードバックしていく。緩和ケアに関する主治医のニーズはさまざまであり，また日々変化することを念頭に置き対応していく。また，より適切な対応部門が他に存在すると考えられる場合には，その当該科の介入を主治医とともに考慮する。緩和ケア医の介入内容は診療録に適宜記載し，病棟看護師を含めた医療チームが情報を共有できるように配慮する。

■表2　緩和ケアコンサルテーションにおける難易度

primary	：すべての医療従事者に求められる基礎の緩和ケア
secondary	：がん治療医には必須とされる緩和ケア
tertiary	：緩和ケア専門医に求められる，より専門的な緩和ケア

■表3　緩和ケアコンサルテーションにおける関わり方のレベル

レベル1	：患者とのコンタクトはなしで，アドバイスのみ（例，電話相談など）
レベル2	：患者とのコンタクトは一時的，もしくは週1～2回程度で，終診も考慮
レベル3	：患者とのコンタクトは継続的で，主治医のニーズに適宜フィードバックできるよう毎日回診する
レベル4	：患者とのコンタクトは継続的で，毎日重点的に回診し主体的に介入する
レベル5	：患者とは主治医として関わる（緩和ケア病棟での関わりに相当）

5) 毎週1回の緩和ケアチーム合同カンファレンスにおいて，緩和ケアチームメンバー全員でチームが関わっている対象患者について検討する。各職種への依頼患者は形式上全員が緩和ケアチームへの依頼にはなるが，実際はすべての患者をチーム全体で共通して継続的に診ているわけではない。ただ，病状の進行に従って終末期に至る過程で，最初のニーズが他のさまざまなニーズとも関連していくようになることから[2]，この合同カンファレンスにおいてお互いに提示し合って，多職種の観点からのアドバイスが適宜受けられるようにしている。

これをそれぞれの患者について継続的に繰り返し行っていくことで，その経過の中で求められている緩和ケアのニーズ（内容）やその難易度に応じてチームとしての関わり方を適時調整する形をとっている。

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ORIGINAL REPORT

Plasma Isoflavone Level and Subsequent Risk of Breast Cancer Among Japanese Women: A Nested Case-Control Study From the Japan Public Health Center-Based Prospective Study Group

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ABSTRACT

Purpose
Because they have large variations in consumption, Asian countries are suitable settings for studies of the effect of relatively high-dose isoflavone intake on breast cancer risk. Nevertheless, no prospective study from Asia has assessed blood or urine levels as biomarkers of isoflavone intake.

Patients and Methods
A total of 24,226 women ages 40 to 69 years in the Japan Public Health Center–based prospective study who responded to the baseline questionnaire and provided blood in 1990 to 1995 were observed to December 2002. During a mean 10.6 years of follow-up, 144 patients newly diagnosed with breast cancer were identified. Two matched controls for each patient were selected from the cohort. Isoflavone levels were assessed by plasma level and food frequency questionnaire, and the odds ratio of breast cancer according to isoflavone level was estimated using a conditional logistic regression model.

Results
We found a statistically significant inverse association between plasma genistein and risk of breast cancer, but no association for plasma daidzein. Adjusted odds ratios for the highest versus lowest quartile of plasma level were 0.34 for genistein (95% CI, 0.16 to 0.74; *P* for trend, .02) and 0.71 for daidzein (95% CI, 0.35 to 1.44; *P* for trend, .54). Median plasma genistein values in the control group were 31.9 ng/mL for the lowest and 353.9 ng/mL for the highest quartile groups. Regarding dietary intake of isoflavones, nonsignificant inverse associations were observed for both genistein and daidzein.

Conclusion
This nested case-control study found an inverse association between plasma genistein and the risk of breast cancer in Japan.

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INTRODUCTION

Soy foods, a traditional staple dish in Asian countries, are a primary source of isoflavones, such as genistein and daidzein, which are classified as phytoestrogens. Because breast cancer risk is substantially lower in Asian than Western countries,[1] the contribution of a high isoflavone intake to low breast cancer risk has been hypothesized.[2] This hypothesis has been supported by in vitro studies at high genistein concentrations and in the majority of animal studies, which together have demonstrated various anticancer effects of isoflavones acting via both estrogen-dependent and -independent mechanisms.[3,4] Estrogen-dependent mechanisms arise through the mediation of estrogen receptor α and β, owing to the similar chemical structure of isoflavones to the human estrogen hormone and their binding affinity to estrogen receptors.[4,5] For this reason, they have been hypothesized to behave like selective estrogen receptor modulators. In contradiction to potential protective effects, however, genistein exhibits estrogenic properties at low concentrations, which could theoretically enhance breast cancer risk.[3,4] In fact, some animal studies have reported that genistein stimulates tumor development and growth.[6,7] Although a recent meta-analysis found that soy intake was associated with a

small reduction in breast cancer risk, the authors concluded that in view of these risk-enhancing effects, recommendations for high-dose isoflavone supplementation to prevent breast cancer or its recurrence were premature.[8] Phytoestrogen supplements, however, are commercially marketed for use by postmenopausal women as natural and safe alternatives to hormone replacement therapy. The effect of relatively high-dose isoflavone on breast cancer risk is now of concern.

Because they have large variations in consumption among individuals, Asian countries serve as suitable venues for studies of the effect of relatively high-dose isoflavone intake on breast cancer risk. Despite this advantage, only a few epidemiological studies on soy or isoflavone intake and breast cancer risk from Asia have been reported.[9] In particular, no prospective study on isoflavone levels in blood or urine samples has been reported, notwithstanding that, because they are partly determined by individual differences in absorption and metabolism, blood or urine levels might better reflect interperson differences than dietary assessment. The three nested case-control studies which have investigated this association in Western populations have been inconsistent, with one reporting an inverse association with plasma genistein in the Netherlands,[10] the second showing no association with urinary genistein in the Netherlands,[11] and the third finding a positive association with urine and serum phytoestrogens in the United Kingdom.[12] This inconsistency might be in part explained by the apparently small variation in isoflavone levels in Western countries. For example, studies in the Netherlands, which has a high incidence of breast cancer (age-standardized rate per 100,000 world population, 86.7 in 2002),[13] reported a median genistein intake of 0.14 mg/d in women ages 49 to 70 years,[14] and a median plasma genistein level of 4.89 ng/mL in the control group of a nested-case control study.[10] In contrast, a study in Japan, where the incidence of breast cancer is low (age-standardized rate per 100,000 world population, 32.7 in 2002),[13] reported a median genistein intake of 22.3 mg/d and median serum level of 90.2 ng/mL.[15] This substantial variation in isoflavone levels suggests that the Japanese population represents an ideal setting for determining whether an association exists at relatively high levels achievable from dietary intake only.

Herein, to clarify the effect of relatively high-dose isoflavone exposure on breast cancer risk, we conducted a nested case-control study within a large-scale population-based prospective study in Japan.

PATIENTS AND METHODS

Study Population

The Japan Public Health Center–based prospective study, which began in 1990 for cohort I and in 1993 for cohort II, included 140,420 subjects (68,722 men and 71,698 women) living in the municipalities supervised by 11 public health centers (PHC). Details of the study design have been described elsewhere.[16] The study protocol was approved by the institutional review board of the National Cancer Center, Tokyo, Japan.

The study population comprised registered Japanese inhabitants living in each PHC area, ages 40 to 59 years in cohort I and 40 to 69 years in cohort II. In this analysis, one PHC area was excluded since data on cancer incidence were not available. We thus defined a population-based cohort of 67,426 women (27,389 in cohort I and 40,037 in cohort II) after the exclusion of ineligible subjects (n = 95).

Questionnaire Survey

A baseline survey was conducted from 1990 to 1994. A total of 55,891 women (83%) returned the questionnaire, which contained questions concerning demographic characteristics, medical history, menstrual and reproductive history, anthropometric factors, physical activity, smoking and drinking habits, and diet.

Blood Collection

Subjects voluntarily provided 10 mL of blood during health check-ups from 1990 to 1995. Blood samples were divided into plasma and buffy layers and stored at −80°C until analysis. Among respondents to the baseline questionnaire, a total of 24,996 women (45%) donated blood.

Follow-Up

All registered subjects were observed from the start of the study period to December 31, 2002. Data on residential relocation were obtained from residential registries. Among study subjects (n = 24,996), 1,289 subjects (5.2%) moved out of the study area and 5 (0.02%) were lost to follow-up within the study at-risk period.

Selection of Patients and Controls

Incidence data on breast cancer were collected for the Japan Public Health Center cancer registry through two data sources—major local hospitals and population-based cancer registries. Death certificates were used to supplement information on cancer incidence. Site of origin and histologic type were coded by members of our study group (Appendix A1, online only) using the International Classification of Diseases for Oncology, third edition, code C500-509. Up to the end of the study period, 144 new breast cancer cases (97 in cohort I and 47 in cohort II) were identified among the 24,226 women (9,689 in cohort I and 14,537 in cohort II) who had returned the baseline questionnaire, reported no history of breast cancer or ovarian cystoma, and provided blood samples. Diagnosis was microscopically verified in 98% of patients, and based on death certificates only in 0.7%. The mortality/incidence ratio was 0.14.

For each patient, two controls were selected using incidence density sampling from subjects who were not diagnosed with breast cancer during the follow-up period when the patient was diagnosed. Control selection was done without reference to incidence of other cancer sites. Controls were matched with each patient for age (within 3 years), PHC area, area (city or town and village), date of blood collection (within 90 days), time of day of blood collection (within 3 hours), fasting time at blood collection (within 3 hours), and baseline menopausal status.

Assessment of Dietary Intake

Dietary intakes of genistein and daidzein were assessed by a food frequency questionnaire of 44 items for cohort I and 52 for cohort II. Isoflavone intake was defined for this study as the sum of genistein and daidzein intake. We documented the questionnaire assessment of isoflavone intake to be reasonably valid (details in Appendix A1).[15,17]

Laboratory Assay

Plasma levels of isoflavone were analyzed using high-performance liquid chromatography with a coulometric array detector in accordance with the modified methods of Gamache and Acworth.[18] Concentrations of genistein and daidzein were determined by linear regression of the peak height for each standard, and adjusted according to the recovery rate of the internal plasma standard. The regression coefficient of peak height and concentration calculated for isoflavones revealed a linearity range of 0 to 0.75 μg/mL, with correlation coefficient values higher than 0.938. Voltametric response for the standard solution displayed coefficients of variation of 8% for intra- and 11% for interday variation. Recovery rates of isoflavones in plasma samples ranged between approximately 73% and 98%. Detection limits were 2.2 ng/mL for genistein and 2.7 ng/mL for daidzein. Laboratory personnel were blinded to case-control status when performing the analyses.

Statistical Analysis

Comparison of baseline characteristics, as well as plasma levels and dietary intake of isoflavones, between cases and controls was evaluated by the Mantel-Haenszel test using matched-set strata. Spearman's correlation coefficients were calculated among plasma levels and dietary intakes of isoflavone

among control subjects. Using a conditional logistic regression model, we calculated odds ratios (ORs) and 95% CIs of breast cancer for plasma levels and dietary intake of isoflavone divided into quartiles based on control distribution. The ORs were adjusted for number of births and age at first birth as potential confounders. The adjusted ORs were calculated based on a total of 405 subjects with complete information for covariates. Linear trends for ORs were tested in the conditional logistic regression model using the exposure categories as ordinal variables. All P values reported are two sided, and significance level was set at $P < .05$. All statistical analyses were performed with SAS software, version 9.1 (SAS Institute Inc, Cary, NC).

RESULTS

Case subjects and controls had significantly different distribution for number of births (Table 1). Other characteristics, such as age at menarche, age at first birth, body mass index (BMI), alcohol consumption, or dietary intake did not substantially differ between the two groups.

Plasma genistein was significantly lower among cases than controls whereas plasma daidzein values were similar (Table 2). No significant differences between the groups were seen for dietary genistein, daidzein, or isoflavone intake. Median isoflavone intake in the control group was 34.8 mg/d (36.1 in cohort I and 29.9 mg/d in cohort II). Genistein and daidzein were highly correlated for both plasma level ($r = 0.72$) and dietary intake ($r = 0.99$). Correlation coefficients between plasma and dietary levels were relatively low for both genistein ($r = 0.23$) and daidzein ($r = 0.31$).

We found a statistically significant inverse association between plasma genistein and the risk of breast cancer (P for trend, .02), but no statistically significant association for plasma daidzein (P for trend, .54; Table 3). Adjusted ORs for the highest versus lowest quartile of plasma level were 0.34 for genistein (95% CI, 0.16 to 0.74; $P \leq .01$) and 0.71 for daidzein (95% CI, 0.35 to 1.44; $P = .34$). Moreover, the results did not change substantially after adjustment for dietary intake of isoflavone or other potential confounders such as age at menarche, menopausal status at baseline, age at menopause, height, BMI, and alcohol consumption. Further, exclusion of cases diagnosed before the first 3 years of follow-up did not substantially change the results, nor did the exclusion of subjects who used vitamin supplements or who provided a nonfasting blood sample (ie, within 6 hours after a meal). Regarding dietary intake, we observed inverse associations for both genistein and daidzein but neither was statistically significant (Table 3). In addition, adjusted ORs by isoflavone intake were closely similar to those by genistein intake (data not shown).

A stratified analysis according to baseline menopausal status showed no remarkable difference between two strata for either genistein and daidzein, regardless of whether the values were assessed by plasma or questionnaire, although the inverse association between plasma genistein and risk of breast cancer tended to be more stable in postmenopausal than premenopausal women (Table 4).

Table 1. Characteristics of Patients and Matched Control Subjects at Baseline

Characteristic	Patients (n = 144) No.	Patients (n = 144) %	Controls (n = 288) No.	Controls (n = 288) %	P*
Mean age, years	51.7		51.8		
Standard deviation	7.1		7.1		—
Family history of breast cancer	2	1.4	2	0.7	.48
Premenopausal women	59	42	118	42	—
Postmenopausal women					
Natural menopause	70	50	140	50	—
Surgical menopause	10	7.2	20	7.2	—
Mean age at menopause, years	50.0		49.8		.76
SE†	0.38		0.27		
Mean age at menarche, years	14.6		14.8		.33
SE†	0.15		0.10		
Mean No. of births	2.3		2.8		.01
SE†	0.12		0.09		
Mean age at first birth, years	25.7		25.0		.22
SE†	0.30		0.21		
Use of exogenous female hormones (current use)	4	3.0	2	0.8	.10
Mean height, cm	151.7		151.4		.70
SE†	0.46		0.33		
Mean body mass index, kg/m^2	23.4		23.5		.49
SE†	0.25		0.18		
Smoking (current smoker)	5	3.5	17	5.9	.23
Alcohol drinking (regular drinker)	18	13	26	9.1	.28
Leisure-time physical activity (≥ once per week)	30	21	57	20	.42
Vitamin supplement user	33	24	61	23	.65
Green tea intake (≥ five cups per day)	36	25	71	25	.42
Mean total energy intake, kcal/d	1,269.4		1,271.0		.41
SE‡	26.5		19.2		
Mean fish and shellfish intake, g/d	45.4		45.7		.75
SE‡	2.5		1.8		
Mean meat intake, g/d	30.5		28.5		.15
SE‡	1.7		1.2		
Mean vegetable intake, g/d	121.2		115.9		.20
SE‡	5.7		4.1		
Mean fruit intake, g/d	104.8		99.4		.79
SE‡	5.9		4.3		

*P for Mantel-Haenszel test with matched-set strata.
†Adjusted for age.
‡Adjusted for age and cohort.

DISCUSSION

In this study, we found a statistically significant inverse association between plasma genistein and the risk of breast cancer, but no association for plasma daidzein. This finding suggests that genistein may

Table 2. Plasma Levels and Dietary Intake of Isoflavone in Patients and Matched Controls

Parameter	Patients (n = 144) Median	Patients (n = 144) Interquartile Range	Controls (n = 288) Median	Controls (n = 288) Interquartile Range	P*
Plasma level					
Genistein, ng/mL	131.8	67.9-202.6	144.5	78.8-255.6	.046
Daidzein, ng/mL	16.7	7.0-34.0	17.9	5.5-40.8	.45
Dietary intake					
Genistein, mg/d	19.9	16.6-24.0	21.7	16.8-26.1	.37
Daidzein, mg/d	12.5	10.1-14.8	13.3	10.3-16.3	.36
Isoflavone, mg/d†	32.5	26.8-38.7	34.8	27.0-42.4	.36

*P for Mantel-Haenszel test with matched-set strata.
†Isoflavone intake = sum of genistein and daidzein intake.

Table 3. ORs and 95% CIs of Breast Cancer According to Plasma Level and Dietary Intake of Isoflavone

Parameter	Quartile 1	2	3	4	*P* for trend
Plasma level					
Median genistein, ng/mL	31.9	108.1	190.8	353.9	
No. of patients	41	37	45	21	
No. of controls	72	72	72	72	
OR	1.00	0.84	1.04	0.46	.07
95% CI	Reference	0.47 to 1.51	0.57 to 1.91	0.23 to 0.91	
Adjusted OR*	1.00	0.69	0.87	0.34	.02
95% CI	Reference	0.36 to 1.32	0.45 to 1.67	0.16 to 0.74	
Median daidzein, ng/mL	0	12.0	27.0	53.7	
No. of patients	30	45	44	25	
No. of controls	72	72	72	72	
OR	1.00	1.50	1.44	0.79	.59
95% CI	Reference	0.85 to 2.64	0.80 to 2.61	0.41 to 1.54	
Adjusted OR*	1.00	1.30	1.51	0.71	.54
95% CI	Reference	0.70 to 2.42	0.80 to 2.86	0.35 to 1.44	
Dietary intake					
Median genistein, mg/d	15.7	18.5	22.9	27.3	
No. of patients	42	36	37	29	
No. of controls	69	75	71	73	
OR	1.00	0.78	0.83	0.58	.15
95% CI	Reference	0.46 to 1.35	0.47 to 1.48	0.30 to 1.12	
Adjusted OR*	1.00	0.81	0.92	0.58	.21
95% CI	Reference	0.46 to 1.45	0.50 to 1.70	0.29 to 1.18	
Median daidzein, mg/d	9.4	11.4	14.1	17.1	
No. of patients	40	39	35	30	
No. of controls	70	74	72	72	
OR	1.00	0.91	0.82	0.65	.21
95% CI	Reference	0.52 to 1.58	0.46 to 1.47	0.33 to 1.27	
Adjusted OR*	1.00	0.96	0.94	0.67	.34
95% CI	Reference	0.54 to 1.74	0.50 to 1.74	0.33 to 1.39	

Abbreviation: OR, odds ratio.
*Adjusted for number of births (0, 1, 2, 3, 4, 5+) and age at first birth (−21, 22-25, 26-29, 30+, nulliparous). Adjusted ORs were calculated based on a total of 405 subjects with complete information of covariates.

play a more important role in the etiology of breast cancer than daidzein. Our findings are in general agreement with those of a recent nested case-control study in the Netherlands,[10] albeit that our inverse association occurred at substantially higher plasma concentrations. For example, median plasma genistein values in the control group of the Netherlands study were 3.75 ng/mL for premenopausal and 4.89 ng/mL for postmenopausal women.[10] In contrast, the median value in our control group was 144.5 ng/mL, and only 3.2% of control subjects was under 5 ng/mL. This apparently high level is not surprising considering that the median value of 353.9 ng/mL in our highest plasma genistein quartile group, which had a significantly lower risk of breast cancer than the lowest group, corresponded to a median dietary intake of 28.5 mg/d for genistein and 46.5 mg/d for isoflavone, as estimated by the validation study data. Although some in vivo and in vitro studies have shown risk-enhancing effects of genistein, our study suggests that relatively high-dose isoflavones exposure achievable from dietary intake alone is associated with a decreased rather than increased risk.

We observed an approximately 65% reduction in breast cancer risk in the highest plasma genistein quartile group but no decrease in the other quartiles, indicating that only the highest group benefited from risk reduction. The apparent lack of a dose-response relationship might imply the presence of a threshold level of effect. Interestingly, this idea contradicts findings in Western populations, in whom inverse associations are seen despite materially low levels of isoflavones. Given the differences in hormonal milieu between the two populations, the potential protective effect of isoflavones in breast cancer might act differently between Western and Asian populations: sex hormone levels are higher in Western than Asian women,[19] for example, as is the prevalence of obesity.[20,21] In this regard, a case-control study in Shanghai found that the inverse association between urinary isoflavone level and breast cancer risk was stronger among women in the high BMI, waist-hip ratio, and estradiol level groups and in the low sex hormone-binding globulin level group than in the respectively converse low and high groups.[22] Alternatively, the apparent lack of a dose-response relationship might merely reflect uncontrolled confounding by other dietary characteristics or risk-lowering behaviors.

The reason for a role for genistein but not daidzein in the etiology of breast cancer is unclear, but several possibilities can be speculated. Genistein possesses stronger binding affinity for estrogen receptor than daidzein.[5] Further, a pharmacokinetic study showed higher plasma levels and a 1.5-fold longer half-life for genistein than daidzein

Table 4. ORs and 95% CIs of Breast Cancer According to Plasma Level and Dietary Intake of Isoflavone By Baseline Menopausal Status

Parameter	Quartile 1	2	3	4	*P* for trend
Premenopausal women					
Plasma genistein, ng/mL					
No. of patients	24	14	19	2	
No. of controls	41	28	25	24	
Adjusted OR*	1.00	0.76	1.75	0.14	.20
95% CI	Reference	0.31 to 1.86	0.68 to 4.50	0.03 to 0.69	
Plasma daidzein, ng/mL					
No. of patients	17	21	15	6	
No. of controls	27	45	23	23	
Adjusted OR*	1.00	0.80	1.27	0.49	.48
95% CI	Reference	0.34 to 1.88	0.48 to 3.38	0.15 to 1.57	
Dietary genistein intake, mg/d					
No. of patients	21	16	14	8	
No. of controls	35	31	32	20	
Adjusted OR*	1.00	0.92	0.86	0.62	.43
95% CI	Reference	0.41 to 2.05	0.34 to 2.18	0.21 to 1.84	
Dietary daidzein intake, mg/d					
No. of patients	20	17	14	8	
No. of controls	36	30	32	20	
Adjusted OR*	1.00	1.07	0.93	0.67	.53
95% CI	Reference	0.46 to 2.51	0.37 to 2.34	0.22 to 2.03	
Postmenopausal women					
Plasma genistein, ng/mL					
No. of patients	17	23	25	15	
No. of controls	28	41	46	45	
Adjusted OR*	1.00	0.54	0.57	0.36	.10
95% CI	Reference	0.18 to 1.62	0.20 to 1.65	0.12 to 1.12	
Plasma daidzein, ng/mL					
No. of patients	13	23	27	17	
No. of controls	40	27	47	46	
Adjusted OR*	1.00	2.86	2.06	1.16	.95
95% CI	Reference	1.03 to 7.98	0.82 to 5.17	0.43 to 3.15	
Dietary genistein intake, mg/d					
No. of patients	20	20	22	18	
No. of controls	33	42	35	50	
Adjusted OR*	1.00	0.73	0.93	0.52	.31
95% CI	Reference	0.30 to 1.77	0.38 to 2.27	0.19 to 1.42	
Dietary daidzein intake, mg/d					
No. of patients	19	22	20	19	
No. of controls	33	42	36	49	
Adjusted OR*	1.00	0.89	0.93	0.64	.43
95% CI	Reference	0.38 to 2.10	0.38 to 2.29	0.23 to 1.72	

Abbreviation: OR, odds ratio.
*Adjusted for number of births (0, 1, 2, 3, 4, 5+) and age at first birth (−21, 22-25, 26-29, 30+, nulliparous).

after ingestion of baked soybean powder containing closely similar amounts of the two.[23] Moreover, the absence of an association for plasma daidzein might be attributable to misclassification arising from the metabolization of this compound. Daidzein can be metabolized by intestinal bacteria to equol and O-desmethylangolites; because approximately only 30% to 50% of individuals are capable of equol production, probably due to differences in gut microflora, daidzein-to-equol metabolizers may have lower plasma daidzein levels than nonmetabolizers.[24] Equol has been suggested to have greater biologic activity than daidzein,[24] and an inverse association between equol level and breast cancer risk has been reported.[25] Here, the lowest plasma daidzein quartile group might conversely have had a lower breast cancer risk than the higher groups due to its inclusion of equol metabolizers, and such misclassification, if present, would lead to a null result.

Our study has several methodological advantages over previous studies of isoflavones and the risk of breast cancer. First, the direct measurement of plasma isoflavone levels provides not only an index of intake but also of the absorption and metabolism of isoflavone, an understanding of which is important to elucidating the mechanisms by which isoflavones might influence breast cancer development. Indirect measurement by dietary intake of genistein is likely a major reason for the present smaller and nonsignificant risk reduction of breast cancer than by plasma genistein. Exposure assessment using

blood samples is therefore likely a more sophisticated means of detecting an association. Second, two case-control studies in Australia and China showed an inverse association between urinary isoflavones and breast cancer risk.[25,26] In view of the retrospective design of these studies, however, blood or urine levels of isoflavones in breast cancer cases might have been influenced by metabolic changes after the breast cancer was detected or by altered eating habits among case subjects. In our nested case-control study within a prospective cohort, in contrast, blood samples were collected before cancer diagnosis, obviating any potential bias due to the presence of cancer. Third, cases and controls were selected from the same cohort, thereby avoiding the selection bias inherent to case-control studies.

Several limitations of this study warrant mention. First, we measured plasma isoflavones only once for each individual. The consumption of soy foods is a personal dietary preference, and intake levels of most individuals are assumed to be relatively stable over time in Japan, as suggested by our validation study, which showed high reproducibility of repeated measurements of genistein intake by food frequency questionnaire (correlation coefficient = 0.72 for 1-year interval and 0.61 for 5-year interval).[15,17] By comparison, plasma isoflavone levels may reflect short-term rather than long-term intake: isoflavones have short half-lives in blood (eg, 6 to 8 hours),[23,27] and plasma levels are particularly affected by time elapsed since the last meal. To minimize the attenuation of risk estimates derived from random measurement errors, we matched fasting time between cases and controls. Second, despite a reasonably large cohort population (24,226 women) and long follow-up period (average, 10.6 years), the number of breast cancer cases was relatively small, reflecting the low incidence rate in Japan (age-standardized rate per 100,000 world population, 32.7 in 2002).[13] The interpretability of our results might therefore be limited, particularly in stratified analyses. Third, although our cohort subjects were selected from the general population, subjects were restricted to the 24,226 women respondents (43%) to the baseline questionnaire who provided blood samples. Although health check-up examinees in our previous report had a different socioeconomic status than nonexaminees and a more favorable lifestyle profile,[28] no apparent difference in isoflavone intake and breast cancer risk factors was found between subjects in the subcohort for this study and the original cohort; median isoflavone intake, for example, was 32.5 and 32.1 mg/d, respectively, and the average number of births was 2.8 and 2.7, respectively.[29] Nevertheless, any extrapolation of the results to the general population should be done cautiously, particularly in view of a previous report showing the difficulty of extrapolating relative risk estimates for a subcohort to an entire cohort. This difficulty might in fact be inherent to prospective studies in general.[30]

Allowing for these methodological issues, we found an inverse association between plasma genistein and the risk of breast cancer in a nested case-control study in Japan. This finding suggests a risk-reducing rather than a risk-enhancing effect of isoflavones on breast cancer, even at relatively high concentrations within the range achievable from dietary intake alone.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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Appendix

The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).

ELSEVIER

Body Size and Risk for Breast Cancer in Relation to Estrogen and Progesterone Receptor Status in Japan

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PURPOSE: The aim of this study is to examine the association of height, weight, and body mass index (BMI) with breast cancer and its hormone receptor–defined subtype in a low-risk population.
METHODS: We identified 441 newly diagnosed cases of breast cancer during a 9.9-year follow-up of a population-based cohort consisting of 55,537 women aged 40 to 69 years. Body size was assessed by using a self-administered questionnaire.
RESULTS: We found a significant positive association of height and marginally significant positive associations of weight and BMI with breast cancer in postmenopausal women. Weight and BMI were associated more strongly with estrogen receptor–positive (ER^+) than ER-negative (ER^-) breast cancer in postmenopausal women. BMI was related significantly to increased risk for ER^+ (hazard ratio [HR] per BMI increment of 1 kg/m^2, 1.08; 95% confidence interval [CI], 1.01–1.15), but not ER^- breast cancer (HR per BMI increment of 1 kg/m^2, 0.95; 95% CI, 0.84–1.06; p for difference of HRs = 0.048).
CONCLUSIONS: The present study suggests that height, weight, and BMI are associated with increased risk for breast cancer among postmenopausal women in Japan. The positive association of weight and BMI might be limited to ER^+ breast cancer.
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KEY WORDS: Breast Cancer, Height, Body Mass Index, Hormone Receptor, Prospective Study.

INTRODUCTION

The incidence rate of breast cancer in Japan has increased sharply during the past three decades (1, 2), although it remains lower than in Western countries (3). Age-standardized rates for 2002, for example, were 32.7 in Japan and 101.1 in the United States (4). This increase may be accounted for by the changing prevalence of Japanese women with such established risk factors as reproductive and anthropometric factors (2). In concrete terms, Japanese women have increased in height from approximately 151 cm in 1975 to approximately 156 cm in 2002 among those aged in their 40s (5) and in the prevalence of overweight individuals as defined by a body mass index (BMI) of 25 kg/m^2 or more from approximately 23% in 1976 to 1980 to approximately 27% in 1991 to 1995 among those aged in their 60s, although it decreased in those younger than 60 years (6). In addition, although the prevalence of obesity, defined as BMI of 30 kg/m^2 or more, is less in Japan (~2% in 1991 to 1995 [6]) than in Western countries (~33% in the United States [7] and ~19% in the European Union [8]), some reports suggested that Asians have a greater percentage of body fat than Western populations of the same age, sex, and BMI (9).

The association between body size and breast cancer risk was studied extensively in Western countries. The majority of earlier studies found a positive association between height and breast cancer risk (10–13). For BMI, an inverse and positive association was observed among premenopausal and postmenopausal women, respectively (10–12, 14). In addition, it was reported that age-specific incidence curves showed different patterns (15), and risk factors (16–20) differed between breast cancer subtypes defined by estrogen (ER) or progesterone receptor (PR) status. However, it remains uncertain whether these associations also occur in Asian populations because only a few Asian studies were performed, even fewer of which were cohort studies. Two cohort studies from Asian countries reported no association between height and breast cancer risk (21, 22). For BMI, one

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Selected Abbreviations and Acronyms

BMI = body mass index
ER = estrogen receptor
PR = progesterone receptor
JPHC Study = The Japan Public Health Center-based Prospective Study
HR = hazard ratio
CI = confidence interval
ER^+ = estrogen receptor-positive
PR^+ = progesterone receptor-positive
ER^- = estrogen receptor-negative
PR^- = progesterone receptor-negative
IGF-I = insulin-like growth factor I
IGFBP = IGF-binding protein

cohort study in Japan showed no association and a positive association for premenopausal and postmenopausal women, respectively (23). In addition, because previous studies suggested that Japanese women are more likely than Caucasians to have ER-negative (ER^-) or PR-negative (PR^-) breast cancer (24–26), it remains uncertain whether associations between body size and breast cancer risk in Asian populations differ between hormone receptor–defined subtypes.

The purpose of the present study is to examine the association of height, weight, and BMI with breast cancer and its hormone receptor–defined subtype separately in premenopausal and postmenopausal women by using data from a large-scale population-based prospective cohort of Japanese women.

METHODS

Study Cohort

The Japan Public Health Center-based Prospective Study (JPHC Study) was launched in 1990 for cohort I and 1993 for cohort II. Study subjects were registered Japanese inhabitants living in several municipalities in each public health center area, aged 40 to 59 years in cohort I and 40 to 69 years in cohort II. Additionally, cohort I included health checkup examinees and cohort II included health checkup examinees and a random sample aged 40 to 69 years from one of the municipalities. Because cancer incidence data were not available, cohort I health checkup examinees (n = 4178) were excluded in this report. Thus, we defined a population-based cohort of 67,426 women, 27,389 in cohort I and 40,037 in cohort II after exclusion of ineligible subjects (n = 95). Details of the study's design were reported elsewhere (27). The JPHC Study was approved by the institutional review board of the National Cancer Center, Tokyo, Japan.

Baseline Questionnaire Survey

A self-administered questionnaire survey was conducted in 1990 for cohort I and 1993 to 1994 for cohort II. A total of 55,891 women (83%; 22,482 [82%] in cohort I and 33,409 [83%] in cohort II) returned the questionnaire, which contained questions concerning their personal and family medical history, menstrual and reproductive history, anthropometric factors, smoking history, habitual intake of foods and beverages (including alcohol), physical activity, and other lifestyle factors. We excluded subjects with a history of breast cancer (n = 354) from baseline questionnaire respondents (n = 55,891), leaving 55,537 women.

Respondents reported their current height (centimeters) and weight (kilograms) at baseline. BMI was calculated as weight (kilograms) divided by squared height (square meters). These self-reported height and weigh data were validated in our previous report (28). For the present analysis, height, weight, and BMI were categorized as listed in Tables 1 and 2.

Follow-Up and Identification of Cancer Cases

All registered subjects were followed up from the start of the study period to December 31, 2002. Data for residential relocation were obtained from residential registries. Among study subjects, 3981 subjects (7.1%) moved out of the study area and 27 subjects (0.05%) were lost to follow-up within the study at-risk period. Death certificates coded according to the requirements of the Ministry of Health, Labor and Welfare were collected through local public health centers. Incidence data for breast cancer were collected through two data sources, major local hospitals and population-based cancer registries. Death certificates were used to supplement the information on cancer incidence. Cancer incidence data were collected for subjects living in the study area only. Site of origin and histologic type were coded by members of our Study Group by using the *International Classification of Diseases for Oncology, Third Edition* codes C500 to 509. Hormone-receptor status was determined in a relatively large number of clinical laboratories, primarily by using enzyme-linked immunoassay, rather than immunohistochemical techniques. Hormone-receptor positivity values were determined as specified by the laboratory that performed the assay, in accordance with the laboratory's written interpretation thereof, or both. Information on extension of breast cancer was used to classify cases into two subgroups: localized cases and advanced cases, defined by a diagnosis of direct extension or metastasis including lymph nodes or other organs. Up to the end of the study period, 441 new breast cancer cases were identified among 55,537 women. Diagnosis was microscopically verified in 97% of cases. The mortality/incidence ratio was 0.13 and the proportion of cases for which information was available from death certificates only was 0.9%.

Statistical Analysis

We excluded 1680 subjects with incomplete information for height, weight, BMI, or menopausal status from 55,537

AEP Vol. 17, No. 4
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TABLE 1. Baseline characteristics by height and BMI category: The Japan Public Health Center-based Prospective Study

	Height (cm)				
	<148	148–151	152–155	156–159	160+
No. of subjects	9907	15,449	14,848	8881	4772
Proportion (%)	18.4	28.7	27.6	16.5	8.9
Weight (kg), mean	49.8	52.7	55.0	56.8	59.2
BMI (kg/m^2), mean	24.0	23.5	23.3	22.9	22.5
Age (year), mean	55.5	52.9	51.0	49.5	48.1
Family history of breast cancer, yes (%)	0.9	1.0	1.1	1.2	1.4
Age at menarche (year), mean	15.4	14.9	14.5	14.3	14.1
Menopausal status, premenopausal women (%)	23.7	34.9	44.2	51.9	60.4
Age at menopause (year), mean	49.2	49.4	49.5	49.4	49.3
Use of exogenous female hormones, current users (%)	0.9	1.0	1.2	1.3	1.5
No. of births, mean	3.0	2.8	2.7	2.5	2.4
Age at first birth (year), mean	25.1	24.8	24.8	24.9	25.1
Smoking status, current smokers (%)	5.1	5.8	6.8	8.3	9.7
Alcohol consumption, ≥100 g/wk ethanol (%)	2.3	3.6	4.3	5.5	6.2
Physical exercise, ≥1×/week (%)	16.3	17.0	18.4	19.4	21.5
Miso soup consumption, ≥3 bowls/day (%)	20.5	18.0	15.4	13.3	11.8
Green vegetable intake, every day (%)	32.4	31.4	30.8	28.2	26.8

	BMI (kg/m^2)						
	<19	19–20.9	21–22.9	23–24.9	25–26.9	27–29.9	30+
No. of subjects	3196	8840	14,161	12,842	8004	5093	1721
Proportion (%)	5.9	16.4	26.2	23.8	14.9	9.5	3.2
Height (cm), mean	153.6	152.9	152.1	151.9	151.2	150.8	149.6
Weight (kg), mean	42.5	47.1	51.1	55.3	59.3	64.1	72.2
Age (year), mean	51.6	50.5	51.4	52.1	52.9	53.3	53.0
Family history of breast cancer, yes (%)	1.0	1.0	1.1	1.1	1.1	0.9	0.7
Age at menarche (year), mean	14.7	14.6	14.6	14.7	14.8	14.9	14.9
Menopausal status, premenopausal women (%)	42.5	47.9	42.8	39.4	35.2	33.0	34.2
Use of exogenous female hormones, current users (%)	0.9	1.0	1.2	1.1	1.3	1.0	1.2
Age at menopause (year), mean	48.8	49.0	49.3	49.5	49.4	49.6	49.3
No. of births, mean	2.3	2.4	2.6	2.8	2.9	3.1	3.2
Age at first birth (year), mean	25.5	25.2	25.0	24.8	24.7	24.6	24.6
Smoking status, current smokers (%)	11.7	8.3	6.5	5.1	5.8	6.1	8.7
Alcohol consumption, ≥ 100 g ethanol /wk (%)	5.7	5.1	4.3	3.6	3.3	3.7	3.0
Physical exercise, ≥1×/wk (%)	15.7	17.6	18.3	18.6	18.7	18.1	16.8
Miso soup consumption, ≥ 3 bowls/day (%)	12.9	14.6	15.5	17.2	18.5	18.6	17.4
Green vegetable intake, every day (%)	29.9	30.1	30.8	30.7	30.6	30.0	30.4

BMI = body mass index.

women, leaving 53,857 women (21,799 premenopausal and 32,058 postmenopausal women), including 430 breast cancer cases (201 premenopausal and 229 postmenopausal women) for inclusion in the analysis.

Person-years of follow-up were calculated from the baseline survey until the date of diagnosis of breast cancer, relocation from the study area, death, or end of the study period (December 31, 2002), whichever occurred first.

The Cox proportional hazards model was used to estimate hazard ratios (HRs) and 95% confidence intervals (CI) of breast cancer by height, weight, and BMI by using the SAS program (PROC PHREG; SAS Institute Inc., Cary, NC). The assumption of the proportional hazards model was checked and found to be satisfied (29). Concerning potential confounders, we used age, area, number of births, age at first birth, and height on the basis of their having been selected by a 10% change-in-estimate strategy (see footnotes to Tables 2 and 3) (30). Other factors, such as a family history of breast cancer in female first-degree relatives, history of benign breast disease, age at menarche, age at menopause, use of exogenous female hormones, smoking status, alcohol consumption, and food intake of such items as meat, vegetables, fruit, and soy foods also were examined as confounders, but not included in the final multivariate-adjusted model. Associations of height, weight, and BMI with hormone receptor–defined subtype were investigated by applying the marginal approach of the model by Wei et al. (31) to the Cox proportional hazards model. In the present study, PROC PHREG simultaneously fits two marginal models: one for hormone receptor–positive and the second for

TABLE 2. Hazard ratio and 95% confidence interval of breast cancer by menopausal status according to height, weight, and body mass index: The Japan Public Health Center-based Prospective Study, 1990–2002

	Height (cm)					
	<148	148–151	152–155	156–159	160+	*p* for trend
Premenopausal women (n = 20,871)[a]						
No. of cases	20	51	53	50	27	
Person-years	25,426	56,589	66,927	45,993	27,857	
Crude incidence rate	78.7	90.1	79.2	108.7	96.9	
Hazard ratio[b]	1.00	1.31	1.15	1.66	1.48	0.08
95% Confidence interval	(Reference)	(0.76–2.24)	(0.67–1.99)	(0.96–2.88)	(0.79–2.74)	
Postmenopausal women (n = 29,168)[a]						
No. of cases	47	68	51	39	24	
Person-years	77,156	102,193	84,427	42,422	18,666	
Crude incidence rate	60.9	66.5	60.4	91.9	128.6	
Hazard ratio[b]	1.00	1.16	1.00	1.64	2.39	0.003
95% Confidence interval	(Reference)	(0.79–1.71)	(0.66–1.52)	(1.05–2.57)	(1.43–3.98)	
	Weight (kg)					
	<50	50–54	55–59	60–64	65+	*P* value
Premenopausal women (n = 20,871)[a]						
No. of cases	49	49	43	25	35	
Person-years	57,171	63,334	49,209	30,158	22,920	
Crude incidence rate	85.7	77.4	87.4	82.9	152.7	
Hazard ratio[c]	1.00	0.89	1.02	0.97	1.57	0.13
95% Confidence interval	(Reference)	(0.59–1.34)	(0.66–1.56)	(0.59–1.61)	(0.96–2.54)	
Postmenopausal women (n = 29,168)[a]						
No. of cases	61	54	49	34	31	
Person-years	91,976	89,579	69,097	43,064	31,147	
Crude incidence rate	66.3	60.3	70.9	79.0	99.5	
Hazard ratio[c]	1.00	0.98	1.02	1.22	1.40	0.053
95% Confidence interval	(Reference)	(0.67–1.43)	(0.68–1.53)	(0.78–1.90)	(0.87–2.26)	
	Body mass index (kg/m^2)							
	<19	19–20.9	21–22.9	23–24.9	25–26.9	27–29.9	30+	*P* value
Premenopausal women (n = 20,871)[a]								
No. of cases	13	35	49	45	27	22	10	
Person-years	13,079	41,753	61,616	52,776	29,636	17,809	6,122	
Crude incidence rate	99.4	83.8	79.5	85.3	91.1	123.5	163.3	
Hazard ratio[c]	1.00	0.94	0.89	0.95	1.07	1.47	1.35	0.19
95% Confidence interval	(Reference)	(0.49–1.80)	(0.47–1.68)	(0.50–1.81)	(0.53–2.13)	(0.72–3.02)	(0.53–3.47)	
Postmenopausal women (n = 29,168)[a]								
No. of cases	10	31	56	62	34	25	11	
Person-years	17,595	46,273	81,743	79,626	53,101	34,921	11,606	
Crude incidence rate	56.8	67.0	68.5	77.9	64.0	71.6	94.8	
Hazard ratio[c]	1.00	1.39	1.43	1.63	1.49	1.56	2.28	0.08
95% Confidence interval	(Reference)	(0.66–2.92)	(0.71–2.91)	(0.81–3.31)	(0.71–3.11)	(0.72–3.38)	(0.94–5.53)	

[a]Number of subjects included in multivariable analysis.
[b]Adjusted for age (continuous), area (10 public health centers), number of births (0, 1,2, 3, 4, and 5+), and age at first birth (<21, 22–25, 26–29, 30+, and nulliparous).
[c]Adjusted for age (continuous), area (10 public health centers), number of births (0,1, 2, 3,4, and 5+), age at first birth (<21, 22–25, 26–29, 30+, and nulliparous), and height (continuous).

receptor–negative breast cancer. Wald test was used to examine the null hypothesis that an estimate from hormone receptor–positive breast cancer equals an estimate from receptor-negative cancer. Linear trends were tested in the Cox proportional hazards models by treating each exposure category as a continuous variable. All *p* reported are two sided, and significance level was set at $p < 0.05$.

RESULTS

In 547,656 person-years for 53,857 study subjects (median follow-up, 9.9 years), 430 newly arising cases of breast cancer were recorded. At baseline, overall mean values for height, weight, and BMI were 151.9 ± 5.59 (SD) cm, 54.0 ± 7.78 kg, and 23.4 ± 3.19 kg/m^2, respectively.

TABLE 3. Hazard ratio and 95% confidence interval of hormone receptor–defined breast cancer according to height, weight, and body mass index: The Japan Public Health Center-based Prospective Study, 1990–2002

	Estrogen receptor positive		Estrogen receptor negative		
	Hazard ratio	95% Confidence interval	Hazard ratio	95% Confidence interval	p^a
Premenopausal women					
No. of cases and subjects	62/20,871		41/20,871		
Height (p/1 cm)[c]	1.03	(0.99–1.07)	1.03	(0.97–1.09)	0.97
Weight (p/1 kg)[d]	1.02	(0.99–1.05)	1.01	(0.97–1.05)	0.64
BMI (p/ 1 kg/m^2)[d]	1.04	(0.98–1.11)	1.02	(0.93–1.13)	0.72
Postmenopausal women					
No. of cases and subjects	65/29,168		41/29,168		
Height (p/1 cm)[c]	1.00	(0.95–1.05)	1.06	(1.002–1.12)	0.11
Weight (p/1 kg)[d]	1.04	(1.01–1.07)	0.98	(0.93–1.03)	0.04
BMI (p/1 kg/m^2)[d]	1.08	(1.01–1.15)	0.95	(0.84–1.06)	0.048
	Progesterone receptor positive		Progesterone receptor negative		
	Hazard ratio	95% Concidence interval	Hazard ratio	95% Confidence interval	p^b
Premenopausal women					
No. of cases and subjects	53/20,871		42/20,871		
Height (p/1 cm)[c]	1.03	(0.98–1.07)	1.04	(0.99–1.09)	0.75
Weight (p/1 kg)[d]	1.03	(0.996–1.05)	1.00	(0.95–1.04)	0.30
BMI (p/1 kg/m^2)[d]	1.06	(0.99–1.13)	0.99	(0.89–1.10)	0.28
Postmenopausal women					
No. of cases and subjects	46/29,168		55/29,168		
Height (p/1 cm)[c]	1.02	(0.96–1.07)	1.03	(0.98–1.08)	0.78
Weight (p/1 kg)[d]	1.03	(0.995–1.07)	1.01	(0.97–1.04)	0.34
BMI (p/1 kg/m^2)[d]	1.07	(0.98–1.16)	1.01	(0.93–1.10)	0.39

BMI = body mass index.
[a]p for the null hypothesis that an estimate from Estrogen receptor–positive equals an estimate from Estrogen receptor–negative.
[b]p for the null hypothesis that an estimate from Progesterone receptor–positive equals an estimate from Progesterone receptor–negative.
[c]Adjusted for age (continuous), area (10 public health centers), number of births (0, 1, 2, 3, 4, and 5+), and age at first birth (<21, 22–25, 26–29, 30+, and nulliparous).
[d]Adjusted for age (continuous), area (10 public health centers), number of births (0, 1, 2, 3,4, and 5+), age at first birth (<21, 22–25, 26–29, 30+, and nulliparous), and height (continuous).

Baseline characteristics by height and BMI are listed in Table 1. Taller subjects tended to be younger, premenopausal, have earlier onset of first menstruation and smaller number of births, and less frequently consume miso soup. Subjects with a greater BMI tended to be postmenopausal and have later onset of first menstruation, larger number of births, and earlier first birth.

HRs and 95% CIs of breast cancer by menopausal status according to height, weight, and BMI are listed in Table 2. Overall, a positive association between height and breast cancer risk was observed for both premenopausal and postmenopausal women (p for trend = 0.08 and p for trend = 0.003, respectively). HRs for women 160 cm or taller compared with those shorter than 148 cm were 1.48 (95% CI, 0.79–2.74) for premenopausal women and 2.39 (95% CI, 1.43–3.98) for postmenopausal women. Marginally positive associations of weight and BMI with breast cancer risk were found for postmenopausal (p for trend = 0.053 and p for trend = 0.08, respectively), but not premenopausal women. The HR for postmenopausal women 65 kg or more compared with those less than 50 kg was 1.40 (95% CI, 0.87–2.26), whereas that for postmenopausal women with a BMI of 30 kg/m^2 or more compared with those less than 19 kg/m^2 was 2.28 (95% CI, 0.94–5.53).

Information on ER and PR status was available for 221 (50%) and 206 (47%) of 441 cases, respectively. Of these, 136 (62%) and 105 (51%) were ER-positive (ER$^+$) and PR-positive (PR$^+$) breast cancer, respectively. The association of body size with hormone receptor–defined breast cancer is listed in Table 3. For premenopausal women, associations of height, weight, and BMI did not differ significantly between ER$^+$ and ER-negative (ER$^-$) breast cancer. However, for postmenopausal women, height was associated more strongly with ER$^-$ than ER$^+$ breast cancer, but the difference was not statistically significant. Conversely, weight and BMI were associated more strongly with ER$^+$ than ER$^-$ breast cancer. BMI was related significantly to increased risk for ER$^+$ (HR, 1.08; 95% CI, 1.01–1.15), but not ER$^-$, breast cancer (HR, 0.95; 95% CI, 0.84–1.06; p for difference of HRs = 0.048). Associations of height, weight, and BMI did not significantly differ between PR$^+$ and PR$^-$ breast cancer for either premenopausal or postmenopausal women.

We conducted additional analyses using the joint classification of ER and PR status (results not listed in tables). The

association of body size did not differ significantly between ER^+/PR^+ and ER^-/PR^- breast cancer for premenopausal women. For postmenopausal women, weight and BMI were associated significantly with increased risk for ER^+/PR^+ (HR per weight increment of 1 kg, 1.04; 95% CI, 1.01–1.08 and HR per BMI increment of 1 kg/m^2, 1.10; 95% CI, 1.01–1.18, respectively), but not ER^-/PR^- breast cancer (HR per weight increment of 1 kg, 0.99; 95% CI, 0.94–1.04 and HR per BMI increment of 1 kg/m^2, 0.98; 95% CI, 0.87–1.10, respectively), although the difference was marginally significant (p for difference of HRs = 0.09 for weight and 0.10 for BMI, respectively). Because of the small numbers of cases, we were unable to adequately assess ER^+/PR^- and ER^-/PR^+ breast cancer cases.

Information on extension of breast cancer was available for 412 of the 441 cases (93%), with 217 cases of localized cancer and 195 of advanced cancer. Additional analyses to investigate whether the association of body size differed between localized and advanced cases showed no significant differences for either premenopausal or postmenopausal women (results not shown).

DISCUSSION

In this large-scale population-based prospective cohort of Japanese women, we found a significant positive association of height and marginally significant positive associations of weight and BMI with breast cancer in postmenopausal women. In addition, weight and BMI were associated significantly with risk for ER^+ breast cancer. To our knowledge, this is the first prospective cohort study to show a significant positive association between height and risk for breast cancer and also examine associations between body size and hormone receptor–defined breast cancer in an Asian population.

The present study shows a positive association between height and breast cancer risk for both premenopausal and postmenopausal women, but the association was more evident for postmenopausal women. This finding is consistent with the majority of findings in Western countries (10–13), but inconsistent with those in Asian countries (21, 22, 32–35). Among studies in the latter, two cohort studies that included 161 and 104 breast cancer cases showed no association (21, 22). For case–control studies, one found no association for either premenopausal or postmenopausal women (32), whereas others found a positive association for one of either premenopausal (33) or postmenopausal women (34, 35), but not both.

Mechanisms underlying the association between height and breast cancer risk were proposed, although they are not fully understood. One possible explanation is the "energy deprivation in early life hypothesis," which is supported by animal studies showing that energy restriction in rodents clearly decreases mammary tumor rates (36). Adult height may serve as an indicator of childhood or adolescent nutrition and energy balance in that short women may have been energy restricted during childhood and adolescence. Women in this study born from 1923 to 1952 might have experienced energy deprivation in childhood and adolescence during World War II. This may have resulted in sufficient variation in energy intake to allow the present detection of a positive association between height and breast cancer risk. Some studies reported a positive association only in populations in which inadequate energy and nutrient intake in childhood and adolescence limited growth (13).

However, nutritional inadequacy may not be the sole factor explaining the observed association between height and breast cancer risk. Rather, the influence of growth hormone, insulin-like growth factor I (IGF-I), or possibly in utero influences on ductal stem cells also may have a role. The trend to tallness in an individual is associated with an earlier growth spurt that might result from better nutrition. The adolescent growth spurt involves stimulation by both growth hormone and sex steroids. The IGFs also have an important role during the peripubertal growth spurt (37), and IGF-I levels in childhood correlated strongly with height (38). Furthermore, adult height and mammary gland mass are likely to be associated positively, albeit weakly, because both reflect overall growth to a certain extent at least. Mammary gland mass is likely to reflect the total number of ductal stem cells that develop in the breast in utero, which would emphasize the importance of prenatal exposure (39).

The present study shows a positive, although only marginally significant, association of weight and BMI with risk for postmenopausal breast cancer. This association was reported repeatedly in both Asian (23, 33, 35, 40) and Western countries (10–12). A recent large-scale cohort study in European countries reported that pooled relative risk per BMI increment of 1 kg/m^2 was 1.03 (95% CI, 1.01–1.05) among postmenopausal women who did not use menopausal hormones at the time of recruitment (12), whereas it was 1.04 (95% CI, 0.996–1.08) in the present study. This indicates that the strength of the association between BMI and breast cancer risk in Japanese might be similar to that in Western countries, although the prevalence of obesity substantially differed between Japan and Western countries. The mechanism behind this increase in risk may reflect an increase in serum concentration of bioavailable estradiol, which results in turn from both an increase in estrogen production by aromatase in adipose tissue and a decrease in serum concentration of sex hormone–binding globulin (41).

The present study shows positive associations of weight and BMI with breast cancer for premenopausal women, although they were not statistically significant. Some studies in Asian countries reported no association (23, 33, 35, 40),