③ コールセンターへの問い合わせ内容
④ 全国連絡会議からの課題（ニュースレター，参加団体での役割）
⑤ 今後の追跡調査について
⑥ 平成25年度同意書の不備に関するJCRSUとの調整
⑦ 契約できていない参加団体にある検診データのJCRSUの対応について

【平成26年度　第12回　定期ミーティング】
平成26年12月４日　　日本臨床研究支援ユニット
① 論文投稿準備とスケジュールの状況報告
② 予後調査・印刷発送実施状況（返信状況・宛先不明）について
③ 予後調査・入力対応予定について
④ リマインドになる仕組みについて
⑤ 調査票問い合わせへの対応について
⑥ 平成25年度の同意書の不備に関するJCRSUの具体的対応について
⑦ 契約できていない参加団体にある検診データに関する進捗について
⑧ 業務完了報告書の提出について

【平成26年度　第13回　定期ミーティング】
平成26年12月19日　　日本臨床研究支援ユニット
① 論文投稿準備とスケジュールの状況報告
② 予後調査・印刷発送実施状況（返信状況・宛先不明）について
③ 予後調査・入力対応と再送スケジュールについて
④ QUOカードの宛先不明等で返送があった方の対応について
⑤ コールセンター問い合わせの対応について
⑥ 平成25年度同意書の不備に関するJCRSUの具体的対応について
⑦ 契約できていない参加団体にある検診データに関する進捗について
⑧ 業務完了報告書の提出について

【平成26年度　第14回　定期ミーティング】
平成27年１月16日　　日本臨床研究支援ユニット
① 予後調査の再送を含めた返信状況について（宛先不備の情報共有）
② 25年度の同意書の不備に関する対応について
③ １月30日の運営委員会内容報告
④ 住民票調査の実施予定について
⑤ コールセンターへ連絡があった同意撤回の対応について
⑥ 契約していない参加団体の検診データ転記について
⑦ 福岡大学病院からの報告
⑧ 原資料の引き上げと保管方法について
⑨ 診療情報提供について

⑩ 論文投稿状況の報告

【平成26年度　第15回　定期ミーティング】
平成27年２月６日　　日本臨床研究支援ユニット

① 予後調査・返信・入力状況
② 26年度予後調査アンケート等以外の送付物について
③ 25年度の同意書の不備に関する対応の進捗
④ 住民票調査の実施状況
⑤ コールセンターへ連絡があった同意撤回の対応報告
⑥ 契約していない参加団体の検診データ転記について
⑦ 福岡大学病院の倫理委員会への報告について
⑧ 参加団体の入力支援依頼について
⑨ 診療情報提供の依頼準備状況
⑩ 論文投稿状況の報告

【平成26年度　第16回　定期ミーティング】
平成27年２月16日　　日本臨床研究支援ユニット

① 予後調査・返信・入力状況
② 26年度予後調査アンケート等以外の送付物について
③ 25年度および26年度の同意書不備に関する対応の進捗
④ 住民票調査の実施状況
⑤ 契約していない参加団体の検診データ転記について
⑥ 参加団体の入力支援依頼について
⑦ 診療情報提供の依頼準備状況
⑧ 論文投稿状況の報告
⑨ 来年度の業務に関する打合せ

～ 月例ミーティング ～

【平成26年度　第１回　J-START月例ミーティング】
平成26年４月９日（水）　東北大学

① 平成26年度申請・交付・状況報告
② データモニタリング委員長離脱に伴う体制再検討について
③ 平成26年度必要な体制の検討（論文化）について
④ 今年度のスケジュール（案）について
⑤ 医療経済研究の費用対効果分析の研究計画について
⑥ 今年度の見積・予算について
⑦ 追跡評価報告書の進捗について
⑧ 福岡大学病院のメール結果について

⑨ 予後調査報告（QUOカード含）について
⑩ 予後調査支払いについて
⑪ 診療情報のJCRSUから参加団体への入力・問い合わせ進捗報告

【平成26年度　第2回　J-START月例ミーティング】
平成26年5月7日（水）　東北大学
① 厚労科研費の連絡と契約の進捗状況
② 乳癌申告データ収集進捗報告
③ 運営委員会の開始時間と調整進捗報告
④ 論文化ミーティングの進捗報告
⑤ データモニタリング統計解析委員会の日程調整について
⑥ 予後調査の返信状況について
⑦ 平成25年度事業実績報告書と研究報告書の提出（5/30締切）の進捗について
⑧ 医療経済研究の費用対効果分析の研究計画進捗報告
⑨ 福岡大学病院の対応の進捗報告

【平成26年度　第3回　J-START月例ミーティング】
平成26年6月4日（水）　東北大学
① 厚労科研費の連絡と契約の進捗状況について
② 5/30論文化ミーティング後の進捗について
③ JCRSUデータクリーニング進捗報告・5/30の課題について
④ 7/16データモニタリング統計解析委員会・7/30研究班運営委員会準備
⑤ 全国連絡会議の日程と内容について
⑥ 予後調査の返信状況・Quoカード送付準備状況報告
⑦ 医療経済研究の費用対効果分析の研究計画・福岡大学病院の対応の進捗報告
⑧ 参加団体の学会発表前の事前報告に関する周知の必要性について
⑨ 事務業務担当者の口コミ募集について
⑩ オープンラボ支払財源について

【平成26年度　第4回　J-START月例ミーティング】
平成26年7月2日（水）　東北大学
① 厚労委託費の進捗と申請書および外部連絡実施状況報告
② 7/16データモニタリング統計解析委員会の出欠・委員長への事前資料準備状況報告
③ 7/30研究班運営委員会の出欠・準備状況報告
④ 論文化進捗状況報告
⑤ データクリーニング進捗報告
⑥（JCRSUでの作業，EDCシステム修正，システムエラーによるデータ相違の報告）
⑦ 全国連絡会議の日程と内容の提案について
⑧ 予後調査の返信状況・Quoカード送付準備状況報告

⑨ 医療経済研究の費用対効果分析について
⑩ 福岡大学病院の対応の進捗報告
⑪ 事務業務パート増員について

【平成26年度　第5回　J-START月例ミーティング】
平成26年8月6日（水）　東北大学
① 厚労委託費の執行について
② 論文化進捗状況報告（クラスター内相関，河合先生との調整について）
③ 全国連絡会議の日程と内容の提案について
④ 予後調査の返信とQuoカード送付準備状況報告
⑤ 医療経済研究の費用対効果分析について
⑥ 福岡大学病院の再同意について
⑦ 事務業務パート増員と業務掌握について

【平成26年度　第6回　J-START月例ミーティング】
平成26年9月3日（水）　東北大学
① 厚労省からの予算連絡と研究実施予定について
② 契約（JCRSU，印刷業者，入力業者，参加団体）について
③ 全国連絡会議の調整進捗報告
④ EDCの個人情報変更管理システムの作成について
⑤ 福岡大学病院データに関する委員長らのご返事報告
⑥ 参加団体内でのJ-START本体研究原資料保管状況と保管契約の報告
⑦ 予後調査の返信用封筒の廃棄について
⑧ 平成26年度後半で実施するべきことの検討（来年度の調査票・がん登録照合について）

【平成26年度　第7回　J-START月例ミーティング】
平成26年10月1日（水）　東北大学
① 倫理委員会への報告完了のお知らせ（議事録について）
② 印刷・入力業者の決定について
③ 予後調査実施予定（対象者抽出・調査票の確認）について
④ 参加団体の入力費請求に関する対応の確認
⑤ 全国連絡会議プログラム案の確認
⑥ 平成25年度予後調査の同意書の不備対応について
⑦ Quoカード発送について
⑧ JCRSU石井さん退職について

【平成26年度　第8回　J-START月例ミーティング】
平成26年11月5日（水）　東北大学
① 予後調査・印刷発送実施状況（返信状況・宛先不明）について

② 予後調査・入力対応状況について
③ 平成25年度同意書の不備に関するJCRSUとの調整
④ 全国連絡会議の準備状況について
⑤ 平成25年度調査票での乳癌罹患申告の医療機関への追加調査実施について
⑥ EDC個人情報入力画面修正について
⑦ 契約できていない参加団体にある検診データについて

【平成26年度　第9回　J-START月例ミーティング】
平成26年12月3日（水）　東北大学
① 予後調査・印刷発送実施状況（返信状況・宛先不明）
② 予後調査の返信数改善案について
③ 予後調査・入力対応予定・書類の不備について
④ コールセンターへの問い合わせに対する回答状況
⑤ 全国連絡会議からの課題（原資料保管）
⑥ 運営委員会出欠状況とプログラムについて
⑦ 平成25年度の同意書の不備に関するJCRSUとの調整
⑧ 契約できていない参加団体にある検診データのJCRSUの対応について

【平成26年度　第10回　J-START月例ミーティング】
平成27年1月7日（水）　東北大学
① 予後調査・返信状況について
② 予後調査・入力と再送スケジュールについて
③ 平成25年度同意書不備に関する対応の進捗について
④ 運営委員会の議題と準備状況報告
⑤ 本年度予算執行計画について
⑥ 契約できていない参加団体との調整状況
⑦ 福岡大学病院の同意書発見と当該参加者への連絡・倫理委員会への報告について
⑧ 個人情報の入力請求に関する確認と周知について
⑨ 事業実績報告書（平成26年度）と継続申請書（平成27年度）の提出について
⑩ 診療情報提供の依頼について

【平成26年度　第11回　J-START月例ミーティング】
平成27年2月4日（水）　東北大学
① 予後調査・返信・入力状況
② 26年度アンケート等以外の参加者からの送付物について
③ 25年度同意書不備に関する対応の進捗
④ 本年度予算執行計画について（①分担研究者・②補遺文書等冊子作成と英文依頼）
⑤ 契約できていない参加団体との調整状況
⑥ 福岡大学病院の同意書発見と当概参加者への連絡・倫理委員会への報告について

⑦ 参加団体の入力支援依頼について
⑧ 事業実績報告書（平成26年度）と平成27年度の研究書類の提出について
⑨ 診療情報提供の依頼について
⑩ 論文のレビューアに対する回答についての進捗

【平成26年度　第12回　J-START月例ミーティング】
平成27年3月4日（水）　東北大学
① 予後調査・返信・入力状況
② 25年度・26年度同意書不備に関する対応の進捗
③ 本年度予算執行確認
④ 参加団体のデータ提供・入力支援について
⑤ 事業実績報告書（平成26年度）と平成27年度の研究書類の提出について
⑥ 論文のレビューアに対する回答についての進捗

～ 研究論文化ミーティング ～

【平成26年度　第1回　J-START論文化ミーティング】
平成26年5月30日（金）　東北大学
① ドラフトの検討（consort参照）
② Table，Appendix内容検討
③ Background
④ 組み入れ図
⑤ 感度特異度発見率
⑥ 発見がんのStage，CRFおよびデータ集積状況

【平成26年度　第2回　J-START論文化ミーティング】
平成26年7月18日（金）　東北大学
① 統計解析・データモニタリング合同委員会（7/16）での討議内容について
② 進捗状況報告とスケジュールの確認
③ Tableの提案等について
④ Background
⑤ 組み入れ図
⑥ 感度特異度発見率
⑦ 発見がんのStage
⑧ CRFおよびデータ集積状況等

【平成26年度　第3回　J-START論文化ミーティング】
平成26年8月27日（水）　東北大学
① 進捗状況報告について

② Table（Primary Endpoint）等について
③ Background
④ 組み入れ図
⑤ 感度特異度発見率
⑥ 発見がんのStage
⑦ CRFおよびデータ集積状況等

【平成26年度　第4回　J-START論文化ミーティング】
平成26年9月12日（金）　東北大学
① 進捗状況報告について
② Table（Primary Endpoint）等について
③ CRFおよびデータ集積状況等

【平成26年度　第5回　J-START論文化ミーティング】
平成26年11月28日（金）　東北大学
① 論文におけるharmの記載について
② 中間期がんの定義の記載について
③ Advanced cancer, invasive cancerの定義の記載について

～ 第42回戦略研究企画・調査専門検討会 ～
（戦略研究追跡評価報告会）

平成26年10月20日　三菱総合研究所
・がん対策のための戦略研究　乳がん検診における超音波検査の有効性を検証するための比較試験報告
出席者　大内憲明，石田孝宣，成川洋子

Ⅲ. 補遺文書

（1）乳房用超音波検査に推奨される超音波画像診断装置について

J-START教育プログラム委員会　　委員　　中島　一毅（JABTS精度管理研究班　班長）
J-START精度管理・安全性評価委員会　委員長　遠藤登喜子
J-START精度管理・安全性評価委員会　委員　　植野　　映
J-START精度管理・安全性評価委員会　委員　　角田　博子

J-STARTの運営において重要な問題として，試験に使用する超音波装置がある。多くの超音波診断装置は汎用超音波画像診断装置として薬事収載されており乳房用超音波画像診断装置というジャンルはない。しかし，前向き臨床試験であるJ-STARTの実施において，試験の精度管理上，装置の精度管理は必須である。そこで，長く乳房用超音波画像診断装置の精度管理研究を続けてきた日本乳腺甲状腺超音波診断会議（JABTS）精度管理研究班での研究結果から，J-STARTでの推奨装置，ひいては乳房用超音波画像診断装置の推奨基準を想定した。

JABTS精度管理研究班の研究では，超音波装置の性能を規定する因子は，方位分解能，時間分解能，スライス厚方向の分解能，コントラスト分解能である。さらに実臨床で検査者の視認性を規定する因子として，モニタの解像度と階調表示性能，検査者の業務負担があげられる。また，検査環境（イルミネーション等）はモニタの視認性に大きな影響を与えることがわかっている。

J-STARTでは要精査基準を仮定しているため，この要精査基準を確実の検出・判断できるように，以下の項目を数値目標として設定した。

- 1mm以上の腫瘤が描出可能である
- 5mm以上の腫瘤に関しては，以下の所見が評価可能である
  - 腫瘤内部エコーの有無が確実に判断可能で，単純嚢胞と腫瘤とが高い精度で鑑別可能である
  - 腫瘤としての形状評価が確実に可能である
  - 腫瘤境界部の評価が十分に可能で，サイズ，DW比の測定が可能である
  - 腫瘤周囲の所見（境界部のバックスキャッタリング，正常乳腺組織外への浸潤状況など）が十分描出され，かつ評価可能である
  - 腫瘤内部の点状高エコーなどの所見が十分に認識可能である
- 低エコー域と正常乳腺の構造が十分区別可能である
- 乳腺内の直径2mm以上の乳管構造が明瞭に描出可能で，乳管内病変の有無，立ち上がりや分布が十分に評価可能である
- 乳管内，低エコー域内の点状高エコーが認識・評価可能である

上記の条件をみたすことを検証するため，JABTS精度管理研究班等で開発した乳房超音波精度管理ファントム，および班員による臨床画像評価を行い，装置の検証を進めた。その結果を基にした推奨装置のリストをJ-START開始当初に報告していたが，参加施設の個別の問題もあるため，公表のみで実際の制限は加えられていない。

今回，J-STARTのまとめとして各参加施設で使用装置された装置を確認するため，装置および探触子使用状況のアンケートを行い，その集計結果から使用された装置リストを作成したので報告する。

また，本臨床研究の進捗により，開発メーカー側も乳房専用超音波画像診断装置の必要性を認識，乳房用超音波装置として開発・販売される装置が増えている。これはJ-STARTによる社会効果と反映すると思われ，本試験の経済活性化の一面も感じている。

今回，開発メーカーに対し，J-START開始時には発売されていなかった新しい装置を含め，現在発売中の乳房用超音波画像診断装置として，特に推奨する装置・探触子を調査し，乳房用超音波画像診断装置リストとして作成したので合わせて報告する。

さらにJABTS精度管理研究班では各超音波画像診断装置・探触子に対し，精度管理ファントムによる画像評価ならびに班員による臨床画像評価を行っているが，現在までに乳房専用超音波画像診断装置としての評価が終了し良好な評価が得られている装置・探触子を参考までに二重丸◎として表記した。まだ未評価の装置は掲載していないので，「未評価＝非推奨」ではないことをお断りしておく。

以下，（1）J-STARTで使用された装置・探触子リストと台数，（2）開発・販売メーカーがマンモグラフィ，乳房超音波併用検診用の乳房用超音波画像診断装置として特に推奨する装置・探触子の一覧表を掲載する。上記したように（2）の表中の二重丸◎は，JABTS精度管理研究班で乳房専用超音波画像診断装置として良好な評価が得られた装置・探触子の組み合わせである（2011年2月18日現在）。

（1）J-STARTで使用された装置・探触子リスト

マンモグラフィ，乳房超音波併用検診の臨床試験において使用された，乳房用超音波画像診断装置・探触子。臨床試験登録症例で使用が報告された装置と台数について以下に列記する。括弧内は使用された台数。（集計結果であるため，装置・探触子の組み合わせ台数は不明）

- 日立メディコ
  - 装置：EUB-7500（26），EUB-8500（7），MyLab25（3）
  - 探触子：EUP-L74M，EUP-L64，EUP-L54M，LA435，LA523E
- 東芝メディカルシステムズ
  - 装置：APLIO XG SSA-790A（10），APLIO XV SSA-770（15），XARIO XG SSA-680A（1），XARIO SSA-660A（20）
  - 探触子：PLT-1204AT，PLT-1204BT，PLT-805AT
- アロカメディカルシステム
  - 装置：ProSound α7（10），ProSound α5（6），ProSound α10（3），Prosound α6（6）
  - 探触子：UST-5412，UST-567，UST-5410，UST-5413，UST-568
- GEヘルスケア・ジャパン
  - 装置：LOGIQ7（6），LOGIQP6（1）
  - 探触子：M12L，11L
- 富士フイルムメディカル
  - 装置：FAZONE M（1）
  - 探触子：L10-5
- フィリップスヘルスケア
  - 装置：HDI-5000（1）

（2）乳房超音波併用検診用の乳房用超音波画像診断装置として開発・販売メーカーが特に推奨する装置・探触子。「○」は「メーカー一押しの乳房超音波用超音波診断装置」として調査したもの。

さらに，二重丸「◎」は現在（2011年2月18日）までに乳房専用超音波画像診断装置としての評価が終了し良好な評価が得られている装置・探触子の組み合わせ。JABTS精度管理研究班の基準は乳房精密検査用の超音波画像診断装置を想定し評価をおこなったものである。未評価の装置・探触子は二重丸「◎」をしていないので，「未評価＝非推奨」ではないことをお断りしておく（2011年2月18日現在)。(「使用環境に制限有」の装置は，モニタの特性上，十分に暗い室内での使用が必須条件)

日立メディコ	Mappie	EUP-L75	EUP-L74M	EUP-L65
HI VISION Ascendus	◎	◎	◎	
HI VISION Preirus	◎	◎	◎	○
HI VISION Avius	−	◎	◎	○

東芝メディカルシステムズ	PLT-1204BX	PLT-1204BT	PLT-805AT
APLIO XG SSA-790A	◎	◎	○
APLIO MX SSA-780A	−	◎	○
APLIO XG SSA-680A	−	◎	○
Viamo SSA-640A（使用環境に制限有）	−	○	○

GEヘルスケア・ジャパン	ML6-15-D	M12L	11L	11L-D
LOGIQ E9	◎			
LOGIQ 7	−	◎		
LOGIQ P6	−		○	
Voluson E8	○			
Voluson E6	−			○

持田シーメンスメディカルシステム	18L6HD	14L5
ACUSON S2000	◎	◎

キヤノンマーケティングジャパン	L15-4
Aixplorer	◎

フィリップスヘルスケア	L15-7
iU22	◎

富士フイルムメディカル	L14-5w
FAZON CB（使用環境に制限有）	○

アロカメディカルシステム	UST-5415	UST-5411	UST-5412	UST-567	UST-5413	UST-568
プロサウンドF75	◎	◎	－	－	－	－
プロサウンドα7	－		○	○	－	－
プロサウンドα6	－	－	－	－	○	○

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Controversies in Breast Cancer Screening for Women Aged 40–49 Years

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Mammography is the only method of breast cancer screening that has established evidence of a mortality reduction. However, mammography does not achieve sufficient accuracy in the high-density breasts of patients <50 years of age. In 2009, the US Preventive Services Task Force revised its recommendation for breast cancer screening in women aged 40–49 years from Grade B to C because the net benefit was relatively small for this age bracket. The net benefit of screening is the sum of benefits and harm and should always be monitored especially in population screening. A high recall rate, an inefficient number needed to invite for screening to prevent one breast cancer death, a high false-positive rate and unnecessary additional imaging for women aged 40–49 years are great concerns of mammography screening. Overdiagnosis is also a detriment of mammography screening; however, it may have a limited effect on women aged 40–49 years. Establishment of new evidence for breast cancer screening, such as ultrasonography screening, is needed in order to create a more effective screening system.

Key words: breast cancer screening – mammography – net benefit – harm – ultrasonography

INTRODUCTION

The purpose of screening is to diagnose patients sooner so their prognosis can be improved through earlier intervention. To assess the effect of a breast cancer screening program, randomized controlled trials (RCTs), which compared mammography screening as an intervention group with a non-intervention control group, have been performed since the 1970s (1–5). A meta-analysis of seven RCTs that included 13 years of follow-up estimated a 16% reduction in breast cancer mortality in the women invited for screening (6). On the basis of this result, many countries have adopted mammography as a national breast cancer screening program. Although the incidence of breast cancer still has been increasing, some countries have successfully reduced breast cancer mortality (7,8). Thus far, screening with mammography has been the gold standard all over the world. On the other hand, since the time screening programs were endorsed, there has been debate, at times, sharply polarized, over the magnitude of their benefit and harm and the balance between them. In 2009, the US Preventative Services Task Force (USPSTF) published its updated guidelines for screening mammography (9). They comprehensively assessed the efficacy of breast cancer screening in terms of the net benefit, which is the sum of benefits (mortality reduction) and harm (radiation exposure, pain, anxiety, overdiagnosis and false-negative and false-positive mammography results). As a result, the USPSTF revised their recommendation for breast cancer screening of women aged 40–49 years from Grade B to C because the net benefit was relatively small for this age bracket. This revised guideline created a sensation among the countries that had recommended mammography screening for women aged 40–49 years. The Canadian Task Force on Preventive Health Care also updated their guidelines for breast screening in 2011 and concluded that the reduction in mortality associated with screening mammography is small for women aged 40–74 years at average risk of breast cancer (10). They also noted a greater reduction in mortality is seen with mammography for women at average risk aged 50–74 years than

among similar women aged 40–49 years; however, harms of overdiagnosis and unnecessary biopsy may be greater for younger women than for older women.

As a result of these debates, it is obvious that there have been controversies in breast cancer screening especially for women aged 40–49 years. Although it is difficult to find the best way to dealing with it, the purpose of the present narrative review is to sort out and clarify the controversies in screening for younger women and to help to seek a solution to this matter.

METHODS

We conducted a literature search using PubMed with the following keywords 'Breast cancer screening' and 'benefit' and 'randomized'. Some review articles published in 2011–2013 were selected as basic reference to investigate older literature. Then we conducted again literature search using PubMed with the following keywords: 'mammography', 'breast cancer', 'screening'; 'randomized', 'premenopausal', '40 years' and 'older than 40'. Literature research period was from 2005 until 2013. We retrieved the individual articles and completed our search using the reference lists of the articles and other review articles. As meta-analyses have already been done and as they include estimates of the effect of screening for different age groups, we did not intend to carry out a new meta-analysis.

BENEFIT OF BREAST CANCER SCREENING (MORTALITY REDUCTION)

For women aged 39–49 years, eight reliable RCTs provided data for a meta-analysis [Health Insurance Plan (HIP) of Greater New York (1), Canadian National Breast Screening Study-1 (2), Stockholm (3), Malmo (3), Swedish Two-County (two trials) (3), Gothenburg (4) and the Age Trial (5)]. Combining results, the pooled relative risk (RR) of breast cancer mortality for women randomly assigned to mammography screening was 0.84 [95% credible interval (CrI), 0.74–0.95], which indicates a 16% reduction in breast cancer mortality and was in favor of screening (5). On the other hand, the estimated RR of breast cancer mortality for women aged 50–59 years and 60–69 years with invited screening was 0.86 (CrI, 0.75–0.99) and 0.68 (CrI, 0.54–0.87), respectively. This result showed that the effect of mortality reduction in women aged 39–49 years is smaller than that of women aged 60–69 years; however, it is almost the same level as that of women aged 50–59 years (9).

Even though RCTs potentially provide the most reliable information on the effect of breast screening, we have to always pay attention to various biases. For example, the trials, except for the Age Trial, were not specifically designed to study the effect of screening in younger women; for those trials in which women younger than 50 years at study entry had been included, it was unclear whether the extent of any benefit in these women was because of screening after they reached 50 years of age. The Age Trial was specially designed to avoid those biases by studying the effect of an annual invitation to mammography starting at age 40 years, compared with that of an uninvited control group (5). After 10.7 years of follow-up, the RR was 0.97 [95% confidence interval (CI), 0.89–1.04] for all-cause mortality and 0.83 (CI, 0.66–1.04) for breast cancer mortality among women randomly assigned to screening. This result did not provide a significant difference regarding breast cancer mortality; however, the trend of the result was consistent with a meta-analysis of previous studies.

In 2009, the USPSTF revised its recommendation for breast cancer screening in women aged 40–49 years from Grade B to C because of an inefficient number needed to invite (NNI) for screening to prevent 1 breast cancer death in this age group (11). The estimated NNI in patients aged 39–49 years was 1904 (CrI, 929–6378) over several screening rounds that varied by trial (2–9 rounds) and 11–20 years of follow-up. The NNI for women aged 50–59 years was 1339 (CrI, 322–7455), and the NNI for those aged 60–69 years was 377 (CrI, 230–1050). Thus, they concluded that the net benefit was smaller for women aged 40–49 years with a larger NNI than that of women aged 50–59 years.

HARM ASSICIATED WITH BREAST CANCER SCREENING

Various consequent events and results associated with breast cancer screening may be considered harmful. The net benefit of screening that is the sum of the benefits and harm should always be monitored especially during population screening. Potential harmful events include the consequences of false-positive and false-negative test results, unnecessary additional imaging, fine-needle aspiration cytology (FNA), biopsy, overdiagnosis, radiation exposure, pain during procedures, patient anxiety and other psychological responses (9).

FALSE-POSITIVE AND FALSE-NEGATIVE MAMMOGRAPHY RESULTS, ADDITIONAL IMAGING AND BIOPSIES

The cumulative risk of false-positive mammography results have been reported ranging from 21 to 49% after 10 mammography examinations for women in general and up to 56% for women aged 40–49 years (12–14). Data from the Breast Cancer Surveillance Consortium (BCSC) for regularly screened women that were based on results from a single screening round indicated that false-positive mammography results were common in all age groups but were most common among women aged 40–49 years (97.8 per 1000 women per screening round). Conversely, screening-detected invasive cancer rates were lowest among women aged 40–49 years (1.8 per 1000 women per screening round) and increased with age (9). Rates of additional imaging were highest among women aged 40–49 years (84.3 per 1000 women per

screening round) and decreased with age. According to data from Japan, the recall rate (9.9%) and false-positive rate (9.6%) were higher among women aged 40–49 years than that of the other age brackets, with statistical significance ($P < 0.001$) (15). These data were consistent with the BCSC data. In Japan, the rates of additional imaging, FNA and biopsy were also significantly higher for women in their 40s than that of the other age brackets ($P < 0.001$), whereas in the BCSC, the biopsy rates were lowest among women aged 40–49 years (9.3 per 1000 women per screening round) and increased with age. The harm, in terms of false positivity, unnecessary additional imaging and biopsy, was highest for women aged 40–49 years in Japan, but less than that of the BCSC in all age brackets. In addition, the cancer detection rate per 1000 screened Japanese women aged 40–49 years was 2.8 that was slightly higher than that of the 2.6 recorded in the BCSC data.

SENSITIVITY

Published data on the sensitivity of mammography screening are limited. To calculate the proper sensitivity of screening, it is necessary to obtain all breast cancer cases that may exist at screening. In the Age Trial, an RCT that was designed specifically to study the benefit of starting mammography screening beginning at the age of 40, the sensitivity of first screening was reported to be 73.6% (5). In data from Japan, Suzuki et al. (16) showed the estimated proper screening sensitivity using a population-based cancer registry. The sensitivity was lowest among women aged 40–49 years (71.4%) and increased with age. Sensitivity among women aged 50–59 years was 85.8% and among those aged 60–69 years was 87.2%. They also demonstrated the sensitivity of mammography in association with different breast densities and ages. Among women 40–49 years of age, the sensitivities in extremely dense and dense breasts were 50.0 and 60.0%, respectively. In women 50–59 years of age, the sensitivities in extremely dense and dense breasts were 50.0 and 66.7%, respectively. In women 60–69 years of age, the sensitivities in extremely dense and dense breasts were 57.1 and 78.6%, respectively.

OVERDIAGNOSIS

Some screening-detected cancers may never progress to be symptomatic in the absence of screening, and some women might die from other cause(s) before the cancer becomes evident (17). Nonetheless, these cancers are treated. This adverse consequence (harm) of screening is called overdiagnosis or overdetection. In general, the purpose of screening is to diagnose the cancer sooner so the prognosis can be improved by earlier intervention; however, earlier detection may cause overdiagnosis. So far, it is difficult to judge whether a particular woman has had an over-diagnosed cancer or whether individual tumors are overdiagnosed. Bleyer et al. (18) argued that whatever the mortality benefit, breast cancer screening involved a substantial harm, as the increased detection of additional early-stage cancers was not matched by a reduction in late-stage cancers. In the USA, the introduction of screening mammography was associated with a doubling in the number of early-stage breast cancer cases that were detected each year, from 112 to 234 cases per 100 000 women, an absolute increase of 122 cases per 100 000 women. Concomitantly, the rate at which women present with late-stage cancer has decreased by 8%, from 102 to 94 cases per 100 000 women, an absolute decrease of eight cases per 100 000 women. With the assumption of a constant underlying disease burden, only eight of the 122 additional early-stage cancers diagnosed were expected to progress to advanced disease.

The most reliable estimate of overdiagnosis was reported in three RCTs, in which women in the control group were not offered screening at the end of the trial. These three trials were the Malmo (19) and two Canadian trials. The trend regarding overdiagnosis was similar in three trials. The estimated rate of overdiagnosis ranged from 16.0 to 22.7% in cancers diagnosed during the screening period in women invited for screening and ranged from 9.7 to 12.4% in cancers diagnosed over a whole follow-up period in women invited for screening (20). Overdiagnosis may have a greater effect on women with shorter life expectancies because of age and comorbidities. Conversely, overdiagnosis may have a limited effect on women aged 40–49 years.

RADIATION EXPOSURE

There were no studies directly evaluating the radiation exposure from mammography screening and consequent breast cancer. As it required, on average, 7 mGy to obtain two-view, bilateral mammography images (21), yearly mammography screening for one decade with the potential of additional imaging would expose an individual to ~60 mGy. A recent case–control study found that for women exposed to diagnostic radiographs for screening or monitoring tuberculosis, the estimated radiation dose was 600 mGy to the breast and patients who had pneumonia or therapeutic radiation for a previous cancer had an increased risk of breast cancer (22). On the other hand, radiation for heart catheterization, scoliosis, back/spine problems, gastrointestinal problems or other unspecified chest radiographs was not associated with an increased risk. There was no study indicating an increased risk from screening mammography radiation, even in those patients exposed at relatively younger ages, from 40 to 49 years.

DISCUSSION

Screening is concerned with the detection of disease at an early stage, with the expectation that treatment will be more effective if begun earlier in the disease process. There is no room for doubt that the principle benefit of screening is mortality reduction; however, the secondary benefits of early

detection, such as an increase in breast-conserving surgery, omission of axillary lymph node dissection with sentinel lymph node biopsy and improved quality of life, might be considered for women with longer life expectancies.

Several randomized trials regarding mammography screening showed the usefulness of mammography screening in women aged 50 years and over with statistical significance; however, the effectiveness in women aged 40–49 years is controversial (23,24) (Fig. 1). In 2009, the USPSTF recommended that starting regular screening mammography before the age of 50 years should be an individual decision that takes the individual patient's context into account, including the patient's values regarding the specific benefits and harm. As background to that recommendation, in terms of the benefit, screening mammography for women aged 40–49 years results in a 15% mortality reduction, and it was acknowledged to have a benefit in eight RCT meta-analyses. On the other hand, the net benefit is smaller for women aged 40–49 years with a larger NNI than that of women aged 50–59 years so the USPSTF revised their recommendation. The Canadian Task Force on Preventive Health Care followed the statement and revised their recommendation for the same reasons (10). Although careful consideration must be given to the net benefit of screening, there are some opposing arguments against the USPSTF (25,26). Saika et al. (27) argued that the USPSTF did not consider different follow-up periods while comparing the NNI by age group. Shorter follow-ups for women aged 40–49 years will lead to a lower cumulative mortality, which results in an overestimation of the NNI. They adjusted for the follow-ups from the trials, and the estimated NNIs for women aged 40–49 years were 1599 with a 15-year follow-up and 1199 with a 20-year follow-up. These NNIs were almost the same level as that of the NNI of 1339 for women aged 50–59 years that were regarded as adequate to start mammography screening.

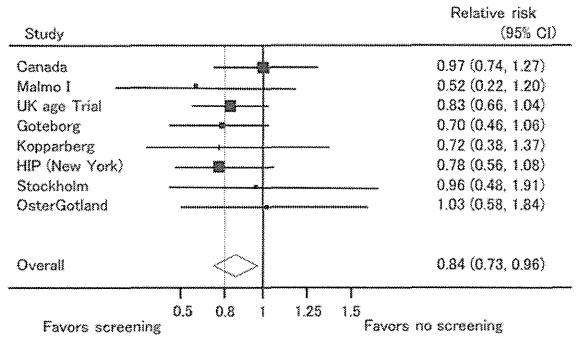

Figure 1. Breast cancer mortality results of the randomized mammography trials in women younger than 50 years [adapted from the Cochrane Review (6)].

The USPSTF also indicated that the recall rate, false-positive rate and unnecessary additional imaging rate were relatively higher for women aged 40–49 years than that of those in other age brackets according to the BCSC data. These data were consistent with that of the data from Japan (15), whereas the biopsy rates were lowest among women aged 40–49 years that increased with age in the BCSC. The harm in terms of false positivity and performance of unnecessary additional imaging and biopsy were greatest for Japanese women in their 40s, but less than that of the BCSC in all age brackets. Thus, screening mammography appeared to be less harmful in Japan than in the USA. A high recall rate, a high false-positive rate and unnecessary additional imaging for women aged 40–49 years were the great concerns of mammography

Table 1. Summary of RCTs of mammography screening

Study (duration)	Screening protocol	Frequency	Age	Screening	Control	Relative risk (95% CI)
HIP (1963–69)	2V MM CBE	12M 4 rounds	40–49 50–64	13 740 16 505	13 740 16 505	0.78 (0.56–1.08) 0.78 (0.60–1.01)
CBNSS-1,2 (1980–87)	2V MM CBE	12M 4–5 rounds	40–49 50–59	25 214 19 711	25 216 19 694	0.97 (0.74–1.27) 1.02 (0.78–1.33)
Stockholm (1981–85)	1V MM	28M 2 rounds	40–49 50–64	14 842 25 476	7103 12 840	0.96 (0.48–1.91) 0.64 (0.41–1.01)
Malmo (1976–90)	1 or 2V MM	18–24M 5 rounds	45–49 50–69	3658 17 430	3769 17 426	0.52 (0.22–1.02) 0.86 (0.64–1.16)
Kopparberg (1977–85)	1V MM	24M 4 rounds	40–49 50–74	9582 29 007	5013 13 551	0.72 (0.38–1.37) 0.55 (0.42–0.73)
Ostergotland (1977–85)	1V MM	24M 4 rounds	40–49 50–74	10 262 28 229	10 573 26 830	1.03 (0.58–1.84) 0.71 (0.56–0.91)
Gothenburg (1982–88)	2V MM	18M 5 rounds	39–49 50–59	11 724 9926	14 217 15 744	0.70 (0.46–1.06) 0.83 (0.60–1.15)
Age (1991–97)	2V then 1V MM	12M 8–10 rounds	39–41	53 884	106 956	0.83 (0.66–1.04)

Relative risk of deaths ascribed to breast cancer, 13-years follow-up.
HIP, health insurance plan; 2V MM, two-view mammography; CBE, clinical breast examination.
[Adapted from the Cochrane Review (6)].

screening, although the age-specific breast cancer incidence must be considered. Breast cancer incidence increases with age in the USA, whereas in Japan, the incidence was highest for women aged 40–49 years (28). Furthermore, mortality because of breast cancer among Japanese women aged 35–64 years is the highest for any type of cancer (28). Therefore, the establishment of an effective screening system for women aged 40–49 years is of great importance in Japan. The Japan Association of Breast Cancer Screening released a statement that it did not follow the USPSTF recommendation because of a different trend with the breast cancer incidence between Japan and the USA and the lack of scientific data on the net benefit of mammography screening in Japan. The benefit of screening can be assessed by a single measure of mortality reduction. With regard to its harm, however, the weight of each criterion differs by country, region, incidence, economic status and personal values. An overall net benefit should be decided according to all these factors.

The sensitivity in the 40–49 age group was significantly lower than that of the other older groups. One of the most important and influential factors is the dense parenchyma in women before menopause. Kolb et al. (29) also showed low sensitivities in dense breast screening and in women <50 years of age of 47.8 and 58.0%, respectively. A great deal of effort has been made to improve the sensitivity in dense breasts; digital mammography may be one of the useful candidates for overcoming this problem. Pisano et al. (30) showed that the overall diagnostic accuracy of digital and film mammography as a means of screening for breast cancer was similar but that digital mammography was more accurate in women under the age of 50 years, women with radiographically dense breasts, and premenopausal or perimenopausal women.

The low sensitivity is one of the essential causes for insufficient effectiveness of the breast cancer screening in the 40–49 age group so that a trial to elevate sensitivity in this age group and dense parenchyma may have larger potential for the improvement than the age group of over 50 years. Another candidate is ultrasonography that can improve sensitivity because it is able to detect breast cancer at an early stage based on mass shape, even in the dense parenchyma of premenopausal women. The American College of Radiology Imaging Network (ACRIN) 6666 is a multicenter protocol to assess the efficacy of screening ultrasonography (31). Twenty-one international centers enrolled high-risk asymptomatic women with dense breasts for three independent annual screening mammograms and ultrasonography. As a result, 40 participants (41 breasts) were diagnosed with cancer: 8 suspicious by ultrasound and mammography, 12 by ultrasonography alone, 12 by mammography alone and 8 participants (9 breasts) by neither. The diagnostic yield for mammography was 7.6 per 1000 screened women (20 of 2637) and increased to 11.8 per 1000 (31 of 2637) for combined mammography plus ultrasound; the supplemental yield was 4.2 per 1000 screened women (95% CI, 1.1–7.2 per 1000). The ACRIN 6666 provided promising data on ultrasonography, but some arguments have been raised regarding the result. The ACRIN 6666 was a small-sized study, and the selected participants were high-risk women. Biases are inevitable in this type of study design; thus, the evidence level remains low. A high-quality center conducted the screening in the ACRIN 6666 so it may be difficult to control the quality of generalization.

The Japan Strategic Anticancer Randomized Trial (J-START) was the first large-scale RCT to verify the quality and effectiveness of ultrasonography for breast cancer screening in women aged 40–49 years (32). The committees carried out an RCT to compare the effectiveness in two screening groups: mammography with ultrasonography (intervention group) and mammography alone (control group). The primary endpoints of this trial were the intergroup comparisons of the sensitivity and specificity, and the secondary endpoint was the intergroup comparison of the accumulated incidence rate of advanced breast cancer during the follow-up period. A total of 76 196 Japanese women aged 40–49 years were enrolled in J-START by the end of fiscal 2010, with the second screening was completed by the end of fiscal year of 2012 (31 March 2013). Publication of the primary and secondary endpoints is expected at the end of 2014 (Table 1).

Endorsement of the new modality can be expected to increase the detection rate; however, it would involve the possibility of increasing the recall rate, which causes detailed examinations. It is necessary to compile data from the J-START regarding false-positive and false-negative test results, unnecessary additional imaging, FNA cytology, biopsy and overdiagnosis, in order to evaluate the net benefit of screening ultrasonography for women aged 40–49 years. The J-START will be able to provide useful evidence regarding cost-effectiveness, quality control and the educational system on screening ultrasonography.

CONCLUSION

A meta-analysis of prior RCTs of mammography screening showed a 15% mortality reduction in the invited women aged 40–49 years. The effect of the mortality reduction in women aged 40–49 years was almost the same level as that of women aged 50–59 years; however, the USPSTF recommends against the routine use of screening mammography for women aged 40–49 years because of its relatively great harm for this age group. It is necessary to evaluate the net benefit of breast cancer screening for women aged 40–49 years. Establishment of new evidence for breast cancer screening such as ultrasonography screening is needed in order to create a more effective screening system.

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Conflict of interest statement

None declared.

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TRIALS

RESEARCH Open Access

Participants' understanding of a randomized controlled trial (RCT) through informed consent procedures in the RCT for breast cancer screening, J-START

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Abstract

Background: It is often difficult to enrol healthy volunteers into a randomized controlled trial (RCT) as there are barriers to participants' proper understanding of a trial. This study aimed to evaluate degrees of understanding of the informed consent (IC) process among healthy volunteers who participated in an RCT. Additionally, factors associated with degree of understanding were investigated.

Methods: The J-START (the Japan STrategic Anti-cancer Randomized controlled Trial) is an RCT investigating the effectiveness of ultrasonography screening for breast cancer in women aged 40 to 49 years. To evaluate participants' understanding of the J-START, we administered questionnaires to 376 Japanese women on the day of enrolment at five study sites across Japan. The respondents were asked to complete the anonymous questionnaire within 2 weeks. We assessed objective understanding and perceived subjective understanding of IC using a Japanese version of the Quality of Informed Consent scale (QuIC). Then we analyzed the characteristics of women whose understanding was poor, and clarified the association between providing information and their understanding of the study protocol.

Results: The average QuIC scores were 78.2 and 82.2 (out of 100 each) for objective and subjective understanding, respectively. These are generally acceptable scores for participants' understanding of an RCT. However, there were four domains with low scores, indicating poor understanding: (1) experimental nature of the study, (2) potential risks or discomfort, (3) benefit to self, and (4) compensation.

Conclusions: Healthy volunteers generally well understood the J-START. Nevertheless, there were some domains in need of improvement. In order to facilitate participants' understanding, it is necessary to provide training to reduce differences in information-providing procedures between medical centres and to endeavour to provide consistent information and conditions.

Trial registration: The J-START was registered with the University Hospital Medical Information Network Clinical Trial Registration (UMIN-CTR), Japan (registration number: UMIN000000757), on July 1, 2007.

Keywords: Breast cancer screening, participant understanding, RCT, informed consent

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Background

It has been suggested that the complex design of a clinical trial, such as a randomized controlled trial (RCT), is difficult to understand for participants. Although participants are enrolled in a trial only after undergoing the informed consent (IC) process, their understanding of the trial in which they are participating is often insufficient [1-9]. The following two factors might account for this insufficient understanding. First, participants cannot distinguish already established, evidenced examination and treatment procedures from study protocols necessitated by treatment that has not yet been established [1-5]. Second, it is difficult to understand the concepts that are characteristic of RCTs, such as randomization and placebos [5-9].

To our knowledge, no large-scale RCT with more than 70,000 healthy volunteers from the general population had been conducted in Japan before the Japan STrategic Anti-cancer Randomized controlled Trial (J-START) was initiated [10]. The J-START is an RCT on the effectiveness of ultrasonography in breast cancer screening that was developed to assess breast cancer screening in Japan in 2007.

According to a survey conducted in Japan on the attitudes of the healthy general population toward clinical trials [11], participation in them is widely recognized as a volunteer activity that provides an opportunity to contribute to society. However, it has been reported that participants do not sufficiently understand the definitions and contents of clinical trials [11]. There are no reports on the understanding of an RCT targeting a general population of healthy women in Japan. Moreover, there are guidelines but no laws about clinical trials except for pharmaceutical products in Japan. Therefore, as a matter of ethics, clinical trials conducted in Japan should make an effort to provide understandable ICs for eligible participants. However, there is no validity of the ICs provided in Japan with respect to ethics compared with trials in other countries. Thus, we surveyed the degrees of objective and subjective understanding of the IC process among J-START participants. Additionally, factors associated with degrees of understanding were investigated. This is a survey study of the quality of IC given to participants of an RCT to clarify what would be helpful for future trials.

Methods

Overview of J-START

J-START is a multi-centre RCT with 42 participating medical centres in 23 prefectures across Japan. It is supported by science research funds from the Japan Ministry of Health Labour, and Welfare. The aim of the J-START is to assess the effectiveness of screenings for breast cancer among women in their 40s. As of 31 March 2011, 76,196 healthy female volunteers had enrolled [12]. The primary endpoints were sensitivity, specificity, and advanced cancer ratio in both screening groups: the intervention group (women who received ultrasonography in addition to mammography) and the control group (women who received mammography only). The research coordinators verbally explained the purpose and method of the RCT to all eligible participants while collecting ICs.

J-START participants were recruited by trained research coordinators. Potential participants were given a supplementary leaflet by mail before visiting the medical centres. At the medical centres, an educational video recording of the study was presented and a verbal description and a booklet were provided for IC. The total time of the educational video was almost 7 minutes, and it played continuously in the visitors' waiting rooms of the medical centres.

Participants and study methods

Of the 42 medical centres participating in J-START, five medical centres in Iwate, Yamagata, Tokyo, Okayama, and Okinawa participated in our study. From 10 November 2010 to 31 January 2011, we distributed anonymous questionnaires to newly enrolled participants regarding their understanding of the RCT at the five medical centres in different Japanese prefectures. At the time we received approval for this survey in September 2010, only the above-cited medical centres were recruiting new participants; furthermore, only those centres had the proper personnel for conducting the accompanying research.

We distributed the anonymous questionnaires regarding participants' understanding of the RCT at the medical centres. Informed consent for participating in our investigation of participants' understanding of the RCT was assumed by response to the questionnaire. The set of documents distributed to each participant included a letter describing the purpose and method of the study, the questionnaire, and a return envelope. Ethical approval was obtained from the Institutional Review Board of Tohoku University Graduate School of Medicine on 27 September 2010 (No. 2010–279).

Questionnaire

Objective understanding (actual knowledge) and subjective understanding (self-assessed understanding) were measured using a Japanese version of the Quality of Informed Consent (QuIC), which is a scale established in the United States to assess participants' knowledge and self-assessment of clinical trials [6]. The items cover the basic elements regarding the protection of human participants as stated in US federal regulations (45CFR46) [13]. In addition to English [6,14-16], the QuIC has been translated into French [17] and Swedish [18]. It has been used not only in clinical trials for developing anticancer agents but also in studies on social support [19] and in a genome cohort study [14].

Part A of the Japanese version of the QuIC contains 16 items measuring actual knowledge of the basic elements of IC. The total QuIC Part A score represents an average of the 16 items on objective understanding, ranging from 0 (lowest) to 100 (highest) [6]. Each item is measured with a triple-bounded binary-choice format: "Totally agree", "Unsure", and "Strongly disagree". The points were given as follows: 100 points for the correct answer, 50 points for "Unsure", which is neither correct nor incorrect, and 0 points for a wrong answer. Answers without a response were marked "No reply". There were four negatively-phrased items, for which the correct answer was "Disagree", so as to avoid agreement bias that might result from all correct answers being "Agree" [6].

Part B of the Japanese version of the QuIC consists of 14 items assessing subjective understanding of important elements of the trial. The total score of the QuIC Part B is an average of the scores for the 14 items [6]. Each item was measured with a quintuple-bounded binary-choice format: 100 points for "Understood very well", 75 points for "Generally understood", 50 points for "Neither understood nor did not understand", 25 points for "Almost did not understand", and 0 points for "Did not understand".

The J-START is an RCT that enrolled healthy volunteers as the participants for breast cancer screening. For that reason, the QuIC questions that pertained only to Phase I clinical studies were deleted (in the original QuIC full version: questions A6, A7, A8, and A10). We then had one Japanese and one Chinese healthcare worker who use English and Japanese on a daily basis translate the remaining questions into Japanese sentences that would be readily understandable in the context of current Japanese culture. Next, we had back-translated that Japanese into English by a different person who used English and Japanese on a daily basis. Finally, that back-translated version was checked by a person whose native language was English. The comprehensibility of the technical terms and expressions in not only the Japanese QuIC, but also the full questionnaire including original items, was checked by having a medical ethics specialist and medical staffers complete the entire questionnaire. We then made revisions to the materials based on their replies. To ensure the validity of the full questionnaire, we evaluated the materials' reliability by test-retest as following. We asked the new participants in J-START, which has the same conditions as the present study, to answer the full questionnaire, including the Japanese version of QuIC and other items, twice, at a 2-week interval. Twenty-one participants answered all the questions in the questionnaire twice. Weighted kappa statistics for QuIC ranged from 0.32 (objective risks) to 0.67 (subjective experimental nature of study), respectively. Cronbach's alpha values for QuIC for internal consistency were 0.57 and 0.89 for Parts A and B, respectively.

Other questionnaires

We administered additional questionnaires to measure age, educational level, marital status, work status, and study allocation of the RCT. These also assessed impressions of materials provided and prior knowledge about J-START and RCTs. These questionnaires and the Japanese QuIC were validated by the pilot study at the same time.

Multimedia information materials had been prepared for J-START (for example, leaflets, educational DVDs). Their effectiveness was assessed with quintuple-bounded binary-choice items ("Very helpful", "Almost helpful", "Neither helpful nor unhelpful", "Almost unhelpful", and "Not at all helpful"). In addition, alternative responses were prepared as follows: "Have not read", and "Have not watched".

The effectiveness of the verbal description during IC was assessed with the following five questions: (1) "The research coordinator facilitated your understanding". (2) "You had an opportunity to ask questions". (3) "You had sufficient time to understand the process". (4) "It was easy to say 'no', if you did not want to continue your participation". (5) "You sought further explanation of the study". The answer to these five questions was coded as follows: 1 for "Yes" and 0 for "No" or "Unsure".

Statistical analysis

Continuous variables are reported with means and standard deviations, whereas categorical variables are reported as percentages. Bivariate correlations were conducted between the QuIC scores and each independent variable. Correlations were assessed using chi-squared tests. All analyses were conducted using SAS statistical software (version 9.3; SAS Institute Inc., Cary, NC, USA).

Results

Participant characteristics

Participant characteristics are shown in Table 1. Of the 745 questionnaires distributed, 376 (50.4%) were returned. Among 376 survey respondents, almost 70% graduated from vocational school, junior college, or above. There were 280 married participants (74.5%), and 308 participants (81.9%) were employed. In relation to group allocation of the RCT, 198 participants (52.7%) were assigned to the intervention group, and 162 participants (43.1%) were assigned to the control group.

Objective understanding

The results of the objective understanding (QuIC Part A) are shown in Table 2. The average QuIC Part A score was