screening modalities of Pap smear and mammography were affected by the intervention and these are the most common programs in Japan,[2,4,21] we assumed that CCS means Pap smear and BCS means mammography (not echography). As the surveys were conducted in early June, "the past 12 months" could include the total intervention term.

Evaluation framework

We used a Difference-in-Differences (DID) approach[22] to evaluate the effect of the intervention on uptake of FCS attendance. Intervention effectiveness can be evaluated by comparing pre- and postscreening attendance in the intervention and comparison groups. However, because crude comparisons of pre- and postoutcomes may be contaminated by the effect of biased characteristics that differ between the two groups, we applied not only the unadjusted DID method but also the covariate-adjusted DID method[23] with a propensity score weight[24] calculated using data on potential covariates such as age and employment status, which mitigated differences in individual traits across intervention and comparison groups.

Covariates

Covariates related to cancer screening attendance were used to present characteristics of study subjects and to control for their possible confounding effects. In line with previous studies,[13,25–30] we used (*i*) household income, (*ii*) age, (*iii*) housing tenure (home-owner or not), (*iv*) employment status, (*v*) marital status (married, never married or widowed/divorced), (*vi*) household structure (living alone, single mother, couple, couple with unmarried child, three-generation family or other), (*vii*) current smoker (yes/no), (*viii*) self-rated health (excellent, very good, good, fair or poor), (*ix*) health checkup in the last year (yes/no), (*x*) regular hospital visit for major physical disease (yes/no), (*xi*) regular hospital visit for obstetric and gynecologic disease (yes/no) and (*xii*) metropolitan areas (yes/no) (see Supporting Information for detailed methods).

For household income, to adjust for family size and composition, the Organisation for Economic Co-operation and Development (OECD)-modified equivalent scale was used with a weight of 1.0 for the first adult, 0.5 for any other household member aged 14 years and over and 0.3 for each child aged below 14 years.[27,31] The study subjects were categorized into quintiles according to the equivalent household income.

Five-year categories of women aged 23–42 and 43–62 years in 2009 were analyzed for CCS and BCS, respectively. This was because women aged 20 years in 2009 were not included for CCS and those aged 40 years in 2009 were not included for BCS, as they were ineligible for cancer screening in 2007 (*e.g.*, women aged 20 years in 2009 were 18 in 2007 and 21 in 2010).

Statistical analysis

Of 34,982 women who were age eligible and had income data, 34,043 noninstitutionalized women (16,044 in 2007 and 17,999 in 2010) were analyzed in this study. The basic characteristics were tabulated according to intervention and comparison groups. The proportion of women in each intervention and comparison group who had attended FCS in the past 12 months was tabulated according to covariates. Chi-square or Fisher's exact tests (when the expected values in any of the cells of a contingency table are below 5) were used to compare the difference in subject characteristics and FCS attendance between intervention and comparison groups. The effect of the intervention on uptake of FCS attendance was estimated by the DID method with unadjusted, age- and income-adjusted and fully adjusted models.

Probability values for statistical tests were two tailed, and $p < 0.05$ was regarded as statistically significant. All statistical analyses, other than inequality indicators, were performed using SAS version 9.2 (SAS Institute, Cary, NC).

Average cost per uptake

For a brief consideration of cost, average cost per uptake[32] of FCS (equally assuming 1 uptake for each CCS and BCS attendance) was calculated by dividing total expenditure by the absolute total number estimate of FCS uptake resulting from the intervention. Total governmental expenditure for the intervention, including additional municipality staff processing costs for the intervention, was reported as 14 billion yen (US$148 million) in 2009.[2] Absolute total uptake was estimated by multiplying the unadjusted, age- and income-adjusted and fully adjusted DID point estimates by census population.[33]

Monitoring inequality indicators

To monitor and evaluate inequality in FCS attendance, attendance inequalities according to household income were calculated because income is a representative socioeconomic factor.[34] Because there is debate about inequality measurement methods, and interpretation of results can change depending on the inequality indicator used, full consideration of the broadest range of measurement was recommended.[35] Therefore, we used absolute and relative indicators of inequality[36]: rate difference, between-group variance and absolute concentration index for absolute inequality and rate ratio, index of disparity, relative concentration index, Theil index and mean log deviation for relative inequality. Detailed explanations of these indicators are given elsewhere (online Supporting Information).[37,38] As these indicators are measured on different scales, we compared the overall change in inequality by calculating the percentage change in each indicator,[36,37] using HD*calc software (version 1.2.1) from the National Cancer Institute.[39]

Results

Basic characteristics of the study subjects are shown in Table 1 (see also Supporting Information Table S1). A statistically significant difference between the intervention and comparison groups was observed in some categories. For example, employment status in 2007 for the CCS group (proportion "not working" was 28.6% for the intervention group *vs.* 32.9% for the comparison group); and marital status, health checkup and

Table 1. Basic characteristics of the study subjects

	Cervical cancer screening group				Breast cancer screening group			
	2007		2010		2007		2010	
Characteristics	Intervention (n=1,465), %	Comparison (n=5,628), %	Intervention (n=1,606), %	Comparison (n=6,146), %	Intervention (n=1,874), %	Comparison (n=7,077), %	Intervention (n=2,000), %	Comparison (n=8,247), %
Household income								
1 st (lowest) quintile	18.4	20.4	20.4	19.9	19.6	20.1	19.3	20.3
2nd quintile	21.2	19.7	19.9	20.0	19.3	20.2	20.6	19.8
3rd quintile	19.0	20.3	18.9	20.3	21.0	19.7	20.8	19.8
4th quintile	21.1	19.7	19.4	20.2	20.5	19.9	20.2	19.9
5th (highest) quintile	20.3	19.9	21.3	19.7	19.6	20.1	19.2	20.2
Age group in 2009[1]								
23–27	19.5	18.6	19.6	18.5	-	-	-	-
28–32	22.7	22.7	23.6	23.4	-	-	-	-
33–37	31.3	29.9	28.8	29.4	-	-	-	-
38–42	26.6	28.8	28.0	28.7	-	-	-	-
43–47	-	-	-	-	21.1	21.5	21.1	21.7
48–52	-	-	-	-	21.1	22.3	21.1	21.4
53–57	-	-	-	-	23.9	25.2	24.5	24.9
58–62	-	-	-	-	33.9	31.1	33.4	32.0
Home owner								
No	34.7	36.0	33.7	32.8	15.4	15.9	16.2	16.0
Yes	65.3	64.0	66.3	67.2	84.6	84.1	83.9	84.0
Employment status								
Not working	28.6*	32.9*	31.5	31.0	30.6	30.4	36.0	34.6
Small scale less than 100 employees	25.9	24.1	25.3	25.8	23.8	23.6	22.0	22.1
Medium scale 100 to 499 employees	12.7	10.9	10.7	13.0	10.3	9.5	8.7	9.3
Large scale more than 500 employees	12.4	11.2	12.6	11.4	7.6	7.3	8.9	8.9
Public office	5.8	4.6	4.4	5.0	5.1	5.0	4.3	4.2
Unknown scale	5.3	4.7	4.1	3.8	4.0	4.2	3.0	3.2
Self-employed/Others	9.0	11.4	11.0	9.7	18.6	19.9	16.7	17.5
Missing	0.3	0.3	0.3	0.3	0.1	0.1	0.6	0.2
Marital status								
Married	55.2	56.5	63.7	63.6	83.6*	83.3*	81.4	82.3
Never married	39.7	38.1	30.8	30.8	4.9	6.4	5.5	6.1
Widowed/Divorced	5.1	5.3	5.5	5.6	11.5	10.3	13.2	11.7
Household structure								
Living alone	3.8	4.8	4.0	4.0	4.8	4.8	6.5	6.2
Single mother	6.7	6.8	6.5	6.9	5.7	6.1	6.3	5.9
Couple	8.0	7.9	8.5	8.0	16.7	18.2	23.3	24.0
Couple with unmarried child	53.4	53.7	56.4	56.8	38.2	37.9	35.2	33.6
Three-generation family	21.7	20.6	18.8	18.5	22.4	21.4	16.5	17.6
Others	6.4	6.1	5.7	5.7	12.3	11.7	12.3	12.7

Epidemiology

Table 1. Basic characteristics of the study subjects (Continued)

	Cervical cancer screening group				Breast cancer screening group			
	2007		2010		2007		2010	
Characteristics	Intervention (n=1,465), %	Comparison (n=5,628), %	Intervention (n=1,606), %	Comparison (n=6,146), %	Intervention (n=1,874), %	Comparison (n=7,077), %	Intervention (n=2,000), %	Comparison (n=8,247), %
Current smoker								
No	78.9	79.7	78.4	79.3	83.4	82.9	78.7	80.3
Yes	18.4	17.6	15.7	15.4	11.6	11.8	9.6	9.5
Missing	2.7	2.7	5.9	5.3	5.0	5.3	11.8	10.2
Self-rated health								
Excellent	22.5	23.2	21.4	20.8	13.9	14.1	12.9*	13.0*
Very good	20.1	18.9	18.6	17.8	15.7	15.6	12.5	14.2
Good	44.5	44.5	41.3	44.1	50.6	49.6	47.5	48.4
Fair	7.6	8.9	9.6	9.3	12.1	11.9	11.6	11.2
Poor	0.8	0.9	1.3	1.2	0.9	1.3	1.7	1.0
Missing	4.6	3.7	7.8	6.9	6.9	7.5	13.9	12.2
Health checkup in the last year								
No	44.4	46.2	40.3	41.6	35.0*	32.6*	29.3	30.1
Yes	53.9	51.5	58.6	57.6	63.2	64.6	68.3	67.7
Missing	1.7	2.3	1.1	0.8	1.8	2.8	2.5	2.1
Regular hospital visit for major physical disease								
No	93.6	95.9	92.2	91.6	77.6	78.0	70.7	72.4
Yes	4.1	2.4	5.5	6.3	19.4	19.5	27.3	25.9
Missing	2.3	1.7	2.4	2.1	3.0	2.5	2.1	1.7
Regular hospital visit for obstetric and gynecologic disease								
No	95.2	95.9	95.6	96.0	96.6*	96.4*	96.7	97.2
Yes	2.5	2.4	2.0	1.9	0.4	1.1	1.3	1.1
Missing	2.3	1.7	2.4	2.1	3.0	2.5	2.1	1.7
Metropolitan areas								
No	81.9	81.7	78.5	78.3	84.4	84.4	82.4	82.7
Yes	18.1	18.3	21.5	21.7	15.6	15.6	17.7	17.3

[1]Categorized by age in 31 March 2009
Note. P values for difference between intervention and comparison groups were obtained using chi-square tests.
*P<.05 The * mark was only placed by the first covariate factor of the characteristic.

regular hospital visit for obstetric and gynecologic disease in 2007 and self-rated health in 2010 for the BCS group.

FCS attendance rates according to basic characteristics are shown in Table 2 (figures are shown in Supporting Information Table S2). In 2007, although overall CCS or BCS attendance rates did not differ significantly between the intervention and comparison groups (21.6 *vs.* 22.5% for CCS; 27.4 *vs.* 29.2% for BCS, respectively), a statistically significant difference for attendance rates between the intervention and comparison groups was observed in the 23–27 years age group (4.2 *vs.* 8.6%), fourth household income quintile (21.7 *vs.* 27.3%), not working (29.1 *vs.* 24.5%), never married (9.0 *vs.* 11.9%), and health checkup yes group (25.3 *vs.* 30.0%) for CCS, first household income quintile (14.4 *vs.* 20.0%) and three-generation family (27.1 *vs.* 32.8%) for BCS. In 2010, the intervention group had significantly higher overall attendance rates than the comparison group (43.3 *vs.* 30.3% for CCS; 43.4 *vs.* 32.5% for BCS, respectively). Similarly, most characteristic categories showed that the intervention group had significantly higher attendance rates than the comparison group, except for small sample categories such as widowed/divorced marital status, living alone and missing.

The increase and DID estimates (effect sizes) of FCS uptake (% point) from 2007 to 2010, according to household income quintile and age group, are shown in Table 3. Although the intervention group had a higher than 15%

Table 2. Cervical and breast cancer screening attendance rates according to basic characteristics

	Cervical cancer screening group				Breast cancer screening group			
	Cervical cancer screening attendance rates				Breast cancer screening attendance rates			
	2007		2010		2007		2010	
Characteristics	Intervention (n=1,465), %	Comparison (n=5,628) %	Intervention (n=1,606), %	Comparison (n=6,146), %	Intervention (n=1,874), %	Comparison (n=7,077), %	Intervention (n=2,000), %	Comparison (n=8,247), %
Overall population	21.6	22.5	43.3[2]	30.3[2]	27.4	29.2	43.4[2]	32.5[2]
Household income								
1 st (lowest) quintile	20.7	17.4	39.3[2]	22.8[2]	14.4[2]	20.0[2]	33.9[2]	24.2[2]
2nd quintile	22.2	21.7	37.2[2]	25.5[2]	26.5	26.2	38.7[2]	27.5[2]
3rd quintile	20.5	22.5	45.7[2]	29.8[2]	26.0	29.8	42.5[2]	30.4[2]
4th quintile	21.7[2]	27.3[2]	44.2[2]	35.5[2]	32.2	33.2	52.0[2]	36.7[2]
5th (highest) quintile	22.6	23.7	49.7[2]	37.8[2]	37.6	36.7	49.9[2]	43.6[2]
Age group in 2009[1]								
23–27	4.2[2]	8.6[2]	33.0[2]	19.9[2]	-	-	-	-
28–32	20.1	18.9	42.7[2]	27.6[2]	-	-	-	-
33–37	23.6	26.2	46.9[2]	34.8[2]	-	-	-	-
38–42	33.2	30.4	47.2[2]	34.5[2]	-	-	-	-
43–47	-	-	-	-	26.3	27.6	50.0[2]	34.8[2]
48–52	-	-	-	-	25.5	29.7	44.7[2]	33.4[2]
53–57	-	-	-	-	29.9	29.6	43.7[2]	32.5[2]
58–62	-	-	-	-	27.4	29.5	38.2[2]	30.3[2]
Home owner								
No	27.1	24.8	45.7[2]	30.3[2]	18.3	19.2	33.4[2]	22.9[2]
Yes	18.6	21.2	42.1[2]	30.2[2]	29.0	31.0	45.3[2]	34.3[2]
Employment status								
Not working	29.1[2]	24.5[2]	43.9[2]	30.0[2]	24.4	25.1	41.6[2]	28.9[2]
Small scale less than 100 employees	19.8	20.6	44.0[2]	27.5[2]	29.0	30.3	46.1[2]	31.4[2]
Medium scale 100 to 499 employees	17.7	20.5	44.8[2]	29.6[2]	25.4	26.9	44.5[2]	36.5[2]
Large scale more than 500 employees	17.0	24.4	41.9[2]	33.2[2]	32.4	34.1	45.2	40.7
Public office	18.8	26.9	62.0[2]	44.1[2]	42.1	52.7	58.1	56.2
Unknown scale	13.0	18.9	22.7	25.2	28.0	29.1	35.0	30.4
Self-employed/Others	22.0	20.8	41.5[2]	31.4[2]	25.3	27.5	41.0[2]	29.6[2]
Missing	0.0	6.7	0.0	10.5	0.0	12.5	9.1	20.0
Marital status								
Married	30.8	29.6	51.1[2]	35.5[2]	28.6	30.6	45.2[2]	33.5[2]
Never married	9.0[2]	11.9[2]	29.3[2]	19.8[2]	19.6	18.1	37.6[2]	25.7[2]
Widowed/Divorced	20.0	22.7	30.7	28.2	21.8	24.1	34.5	29.0
Household structure								
Living alone	16.1	22.7	36.9	34.8	14.4	21.6	35.4	28.7
Single mother	15.3	17.0	32.4[2]	20.9[2]	22.6	21.0	33.6	28.0
Couple	36.8	32.7	60.6[2]	41.2[2]	28.1	28.8	44.6[2]	32.8[2]
Couple with unmarried child	23.1	22.9	43.4[2]	30.4[2]	27.1	29.2	44.7[2]	31.0[2]
Three-generation family	16.7	19.8	40.4[2]	27.8[2]	27.1[2]	32.8[2]	45.0[2]	36.0[2]
Others	16.0	21.2	42.9[2]	29.7[2]	34.8	30.5	44.3[2]	34.9[2]

Epidemiology

Table 2. Cervical and breast cancer screening attendance rates according to basic characteristics (Continued)

	Cervical cancer screening group				Breast cancer screening group			
	Cervical cancer screening attendance rates				Breast cancer screening attendance rates			
	2007		2010		2007		2010	
Characteristics	Intervention (n=1,465), %	Comparison (n=5,628) %	Intervention (n=1,606), %	Comparison (n=6,146), %	Intervention (n=1,874), %	Comparison (n=7,077), %	Intervention (n=2,000), %	Comparison (n=8,247), %
Current smoker								
No	22.1	23.5	45.8[2]	32.7[2]	29.1	31.3	45.9[2]	35.1[2]
Yes	20.4	19.7	37.7[2]	21.8[2]	18.3	17.5	33.0[2]	19.9[2]
Missing	12.5	9.9	24.2	18.4	19.1	21.3	35.2[2]	24.1[2]
Self-rated health								
Excellent	17.6	20.6	45.6[2]	30.4[2]	23.8	28.8	43.8[2]	34.0[2]
Very good	23.4	25.4	43.1[2]	33.1[2]	28.9	31.8	44.4[2]	35.0[2]
Good	23.6	20.6	43.7[2]	30.3[2]	28.6	29.4	45.9[2]	33.7[2]
Fair	20.7	33.1	48.1[2]	31.2[2]	28.2	29.9	40.3[2]	29.8[2]
Poor	45.5	25.0	40.0	26.4	31.3	22.3	57.6[2]	23.8[2]
Missing	10.4	15.9	29.6	21.4	20.2	22.8	34.5[2]	26.4[2]
Health checkup in the last year								
No	17.8	15.2	27.0[2]	15.5[2]	5.6	4.7	14.2[2]	7.3[2]
Yes	25.3[2]	30.0[2]	55.3[2]	41.3[2]	40.2	42.7	57.3[2]	44.7[2]
Missing	0.0	0.0	0.0	2.0	0.0	2.5	6.1	1.7
Regular hospital visit for major physical disease								
No	21.4	22.2	43.9[2]	30.0[2]	27.0	28.9	42.5[2]	31.9[2]
Yes	30.0	32.6	39.8	36.4	29.2	31.3	46.2[2]	34.7[2]
Missing	11.8	11.5	26.3	24.4	25.0	21.1	39.0	24.5
Regular hospital visit for obstetric and gynecologic disease								
No	20.9	22.0	43.0[2]	29.8[2]	27.5	29.2	43.5[2]	32.4[2]
Yes	56.8	52.2	75.0	63.2	25.0	40.0	46.2	49.4
Missing	11.8	11.5	26.3	24.4	25.0	21.1	39.0	24.5
Metropolitan areas								
No	21.4	22.4	42.5[2]	29.8[2]	28.4	29.9	43.8[2]	32.8[2]
Yes	22.3	23.0	46.0[2]	32.1[2]	21.9	25.2	41.4[2]	30.9[2]

[1]Categorized by age in 31 March 2009

Note. P values for difference between intervention and comparison groups were obtained using chi-square or Fisher's exact tests.

[2]P<.05

point increase in FCS attendance rates (21.7% point for CCS and 16.0% point for BCS), there was a 7.8% point (95% confidence interval: 6.2–9.4) increase for CCS and 3.3% point (1.9–4.8) for BCS in the comparison group. DID estimates for overall population were 13.9% point (12.2–15.7) in the unadjusted model, 13.9% point (9.6–18.2) in the age- and income-adjusted model and 13.8% point (9.5–18.1) in the fully adjusted model for CCS and 12.7% point (10.9–14.5) in the unadjusted model, 9.8% point (5.7–13.9) in the age- and income-adjusted model and 9.8% point (5.7–13.9) in the fully adjusted model for BCS. The observed effect (uptake) according to income quintile was not proportional across the quintiles, that is, for CCS, the third income quintile had the highest DID estimate, whereas the second quintile had the lowest with nonsignificance in the covariate-adjusted models. For BCS, the first–fourth income quintiles significantly showed positive values in the DID estimates, whereas the fifth quintile did not show positive values in the covariate-adjusted models (noting wide confidence interval), that is, 5.4% point (3.5–7.3) in the unadjusted model, 0.5% point (−9.8 to 10.9) in the age- and income-adjusted model and 2.6% point (−7.8 to 13.0) in the fully adjusted model for the

Table 3. Increase of cancer screening attendance, unadjusted and covariate-adjusted Difference-in-Differences estimates and 95% confidence intervals from 2007 to 2010

	Increase (95%CI), % point		Unadjusted DID	Age- and income-adjusted DID	Fully-adjusted DID
	Intervention	Comparison	Estimate (95%CI), % point	Estimate (95%CI), % point	Estimate (95%CI), % point
Cervical cancer screening					
Overall population	21.7 (18.5–24.9)	7.8 (6.2–9.4)	13.9 (12.2–15.7)	13.9 (9.6–18.2)[1]	13.8 (9.5–18.1)[4]
Household income					
1st (lowest) quintile	18.6 (11.4–25.8)	5.4 (2.1–8.6)	13.2 (11.6–14.9)	16.9 (7.6–26.3)[2]	17.3 (7.9–26.7)[5]
2nd quintile	15.0 (8.0–22.0)	3.8 (0.4–7.3)	11.2 (9.5–12.9)	8.6 (−0.6–17.8)[2]	8.1 (−1.2–17.3)[5]
3rd quintile	25.2 (17.9–32.6)	7.3 (3.8–10.8)	17.9 (16.2–19.7)	18.0 (8.1–28.0)[2]	17.9 (7.9–27.9)[5]
4th quintile	22.6 (15.4–29.7)	8.2 (4.5–11.9)	14.4 (12.6–16.2)	11.1 (1.2–21.0)[2]	11.4 (1.5–21.2)[5]
5th (highest) quintile	27.2 (20.0–34.3)	14.1 (10.4–17.8)	13.0 (11.2–14.8)	15.2 (5.1–25.2)[2]	14.6 (4.7–24.6)[5]
Age group in 2009[7]					
23–27	28.8 (23.1–34.5)	11.3 (8.4–14.1)	17.5 (16.2–18.9)	17.8 (10.6–24.9)[3]	17.3 (10.3–24.3)[6]
28–32	22.6 (16.0–29.2)	8.6 (5.5–11.8)	14.0 (12.3–15.7)	14.2 (5.4–23.0)[3]	13.2 (4.5–21.8)[6]
33–37	23.3 (17.3–29.3)	8.7 (5.6–11.7)	14.6 (12.8–16.4)	12.6 (4.2–20.9)[3]	12.7 (4.5–21.0)[6]
38–42	14.1 (7.5–20.6)	4.0 (0.9-7.2)	10.0 (8.1–11.9)	12.2 (2.9–21.6)[3]	13.3 (4.0–22.7)[6]
Breast cancer screening					
Overall population	16.0 (13.1–19.0)	3.3 (1.9-4.8)	12.7 (10.9–14.5)	9.8 (5.7–13.9)[1]	9.8 (5.7–13.9)[4]
Household income					
1st (lowest) quintile	19.5 (13.6–25.4)	4.2 (1.3–7.2)	15.3 (13.6–16.9)	12.7 (5.2–20.3)[2]	12.6 (5.0–20.1)[5]
2nd quintile	12.2 (5.6–18.7)	1.3 (−1.9-4.4)	10.9 (9.1–12.7)	10.6 (1.8–19.4)[2]	9.3 (0.4–18.1)[5]
3rd quintile	16.6 (10.2–23.0)	0.6 (−2.6-3.9)	16.0 (14.1–17.8)	12.7 (3.8–21.6)[2]	13.7 (5.0–22.5)[5]
4th quintile	19.8 (13.0–26.5)	3.5 (0.1–6.9)	16.3 (14.4–18.2)	12.0 (2.1–21.9)[2]	11.6 (1.8–21.4)[5]
5th (highest) quintile	12.3 (5.2–19.3)	6.9 (3.4–10.3)	5.4 (3.5–7.3)	0.5 (−9.8–10.9)[2]	2.6 (−7.8–13.0)[5]
Age group in 2009[7]					
43–47	23.7 (17.2–30.1)	7.2 (4.1–10.4)	16.4 (14.6–18.3)	13.1 (4.0–22.1)[3]	12.1 (3.0–21.3)[6]
48–52	19.2 (12.8–25.6)	3.7 (0.5–6.8)	15.5 (13.6–17.3)	13.8 (4.9–22.6)[3]	13.6 (4.8–22.4)[6]
53–57	13.8 (7.7–19.9)	3.0 (0.0–5.9)	10.8 (9.0–12.6)	8.9 (0.4–17.4)[3]	10.0 (1.5–18.5)[6]
58–62	10.8 (5.8–15.9)	0.8 (−1.8-3.3)	10.1 (8.3–11.9)	5.7 (−1.2–12.7)[3]	4.8 (−2.0–11.6)[6]

[1]Adjusted for household income quintile, age group.
[2]Adjusted for age group.
[3]Adjusted for household income quintile.
[4]Adjusted for household income quintile, age group, housing tenure, employment status, marital status, household structure, current smoker, self-rated health, health checkup in the last year, regular hospital visit for major physical disease, regular hospital visit for obstetric and gynecologic disease, and metropolitan areas.
[5]Adjusted for age group, housing tenure, employment status, marital status, household structure, current smoker, self-rated health, health checkup in the last year, regular hospital visit for major physical disease, regular hospital visit for obstetric and gynecologic disease, and metropolitan areas.
[6]Adjusted for household income quintile, housing tenure, employment status, marital status, household structure, current smoker, self-rated health, health checkup in the last year, regular hospital visit for major physical disease, regular hospital visit for obstetric and gynecologic disease, and metropolitan areas.
[7]Categorized by age in 31 March 2009.
Abbreviations, DID; Difference-In-Differences, CI; confidence interval

fifth quintile. Women in the older age group generally indicated lower estimates for both CCS and BCS than the younger, with the oldest age group for BCS representing non-significant positive value in the covariate-adjusted models, that is, although the 23–27 years age group had 17.3–17.8% point of DID estimates for CCS, the 38–42 years age group had 10.0–13.3% point; although the 43–47 years age group had 12.1–16.4% point of DID estimates for BCS, the 58–62 years age group had 4.8–10.1% point.

In the calculation for average cost per uptake, using the results of the unadjusted DID estimates according to age, the absolute total number of uptakes of FCS attendance in Japan resulting from the intervention was estimated as 1.20 million. Thus, the average cost per uptake was estimated as 11,600

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yen (approximately US$123). When the age- and income-adjusted or fully adjusted DID estimates were applied, the average cost per uptake was 13,100 yen (US$139) or 13,400 yen (US$142), respectively.

Table 4 shows estimates and percentage changes of inequality indicators for FCS attendance according to household income quintile within each intervention and comparison group in 2007 and 2010. In the CCS groups all absolute and relative inequality indicators increased, with a wide range, among both the intervention and comparison groups. In the BCS comparison group, although three absolute inequality indicators slightly increased, ranging from 15.9 to 43.9%, five relative indicators did not materially change with negative value for rate ratio. In the BCS intervention group, all indicators decreased, ranging from −12.9 to −74.1%.

Discussion

The cost-removal intervention, which uses distribution of vouchers combined with small media, has increased CCS attendance by 13.9% point and BCS attendance by 9.8% point according to the age- and income-adjusted DID model in Japan, which is a developed country with a low FCS attendance rate. Using the results of income-adjusted DID estimates according to age, the absolute total number of women attending BCS in Japan as a result of the intervention was estimated as 472,000. The total number of deaths that could be avoided by the increase in BCS attendance was calculated as 461 (based on the calculations for total screening numbers required to avoid one death[40]). According to national vital statistics, 12,204 women died from breast cancer in 2010[41]; hence, the avoidable number represents 3.8% of annual cause-specific death by breast cancer. As the number needed to screen for CCS was not available, we used the detection rates for cervical cancer by CCS by age groups according to the Japanese government report for health promotion project in 2009,[42] and the number of cases detected due to the increase in CCS attendance (13.9% point) was estimated as 519. This can reduce death and preserve fertility.[43]

As described in the introduction, although out-of-pocket cost reduction has been recommended for BCS, there is a gap in the evidence as to whether such an intervention will increase attendance for CCS, especially in Asian countries.[7] This study contributes evidence to this field with special consideration of inequality and cost. Implementation of this policy needs considerable spending, with an average cost of more than US$100 per uptake. This is more expensive than most other intervention modalities for increasing FCS, such as client reminders or one-to-one education.[44,45] Previous research has shown that even small out-of-pocket costs decrease the use of preventive care services.[46] In particular, for women of low socioeconomic position, cancer screening may be an unaffordable luxury, with competing out-of-pocket medical and nonmedical expenses, including prescription drugs, dental care and eating out.[7] Elimination of out-of-pocket costs for cancer screening access might be more favorable than reduction but needs a larger budget.

The intervention not only improved overall FCS attendance but also affected the magnitude of inequality in attendance.[47] Although the intervention might increase inequality for CCS, it might decrease inequality for BCS, in accordance with existing literature.[8,47] A number of possible reasons exist for this. First, there were inequalities that had already increased before the intervention, that is, the magnitude of inequality in 2007 was small for CCS but relatively large for BCS. Therefore, inequality variations might widen for CCS but narrow for BCS. Second, related to the first point, different personal compositions, such as age, marital status and regular hospital visit, might cause a difference between CCS and BCS. Elderly affluent women might have attended BCS before the intervention. Women in the highest income quintile might therefore show a lower attendance increase for BCS resulting from the intervention than those in other quintiles. The early years of public health interventions such as FCS are often damaging in terms of health equity.[47,48] The inverse equity hypothesis of Victora *et al.*[49] proposes that affluent sections of society preferentially benefit from, or exploit, such interventions, leading to an initial increase in inequalities (early stage). Deprived sections only begin to catch up once affluent sections of society have extracted the maximum possible benefit (late stage).[50] The younger CCS group may be in the early stage of the FCS intervention (younger women might have less time for FCS due to busy schedules than older women) and the older BCS group may be in the late stage. Third, lack of knowledge about cancer is a predictor of nonattendance at cancer screening.[29] Because different levels of knowledge about FCS are expected among the CCS and BCS groups according to their different characteristics such as age, the small media intervention, often combined with cost-removal vouchers,[7] might differently influence the CCS and BCS groups. However, the impact of this is uncertain because data on the separate effects of small media were unavailable. In a previous study, the educational intervention was less effective than cost removal among the low-income population,[51] whereas lack of knowledge was a more significant reason for nonattendance than economic obstacles among the high-income population.[29,52]

In terms of inequality indicators, not only absolute but also relative inequality indicators showed consistent trends, indicating the robustness of the results for inequality trend[35] as the strength of this study. Inequality indicators can lead to contradictory conclusions on whether inequalities in health have narrowed or not.[37] In fact, relative and absolute approaches inevitably contradict each other when populations have the same proportionate reductions in risk. As the different approaches can lead to very different priorities for action, some researchers suggest absolute indicators deserve primacy.[53] All indicators provide mathematically accurate measures of the change in overall inequality among these populations, but they reflect different normative judgments about what to consider when measuring equality.[35] As 180° opposite interpretations can emerge when using only biased

Table 4. Estimates and percent change of inequality indicators for cancer screening attendance according to household income quintile within each of intervention and comparison groups

	Intervention			Comparison		
Inequality indicators	2007 Estimate (95%CI)	2010 Estimate (95%CI)	Percent change, %	2007 Estimate (95%CI)	2010 Estimate (95%CI)	Percent change, %
Cervical cancer screening group						
Rate Difference[1]	2.06 (−4.66-8.77)	12.52 (5.03–20.01)	509.2	9.90 (6.48-13.32)	15.06 (11.46-18.67)	52.1
Between-Group Variance[1]	0.64 (−6.61-7.89)	20.18 (−2.78-43.15)	3063.8	10.25 (3.15–17.35)	32.81 (19.59-46.04)	220.1
Absolute Concentration Index[1]	0.25 (−0.95-1.45)	2.22 (0.88-3.57)	787.4	1.46 (0.86-2.07)	3.21 (2.57-3.86)	119.7
Rate Ratio	1.10 (0.80-1.50)	1.34 (1.12-1.60)	235.9	1.57 (1.34-1.84)	1.66 (1.46-1.88)	16.4
Index of Disparity	5.68 (−18.91-30.26)	16.27 (2.73-29.82)	186.7	21.93 (9.44-34.43)	24.97 (15.35-34.59)	13.8
Mean Log Deviation	0.69 (−2.99-4.37)	5.44 (−0.41-11.29)	688.5	10.48 (3.31-17.64)	18.27 (10.84-25.70)	74.4
Theil Index	0.69 (−2.98-4.36)	5.41 (−0.36-11.18)	685.6	10.24 (3.37-17.12)	18.00 (10.81-25.20)	75.7
Relative Concentration Index	1.16 (−4.43-6.76)	5.14 (2.02–8.26)	342.0	6.49 (3.82-9.16)	10.61 (8.48-12.73)	63.5
Breast cancer screening group						
Rate Difference[1]	23.16 (17.04–29.28)	18.04 (11.26-24.83)	−22.1	16.69 (13.44-19.95)	19.35 (16.20–22.49)	15.9
Between-Group Variance[1]	58.61 (29.38–87.83)	44.88 (15.43–74.34)	−23.4	33.31 (21.40–45.23)	47.95 (33.81-62.09)	43.9
Absolute Concentration Index[1]	4.12 (3.02–5.22)	3.59 (2.38-4.80)	−12.9	3.24 (2.65-3.82)	3.85 (3.28-4.41)	18.8
Rate Ratio	2.60 (1.96-3.45)	1.53 (1.30-1.81)	−66.9	1.83 (1.62-2.08)	1.80 (1.63-1.99)	−4.3
Index of Disparity	34.10 (15.52-52.68)	20.62 (8.41-32.83)	−39.5	25.64 (16.50-34.77)	31.85 (24.22–39.48)	24.2
Mean Log Deviation	46.98 (21.37–72.59)	12.17 (4.16–20.17)	−74.1	21.26 (13.32-29.19)	22.10 (15.58-28.62)	4.0
Theil Index	42.09 (21.20–62.98)	12.00 (4.23-19.77)	−71.5	20.26 (13.00–27.53)	22.27 (15.77-28.76)	9.9
Relative Concentration Index	15.05 (11.08–19.02)	8.27 (5.47-11.07)	−45.0	11.10 (9.09–13.10)	11.84 (10.09–13.58)	6.7

[1]Absolute indicator for inequality
Positive percent change means widening the inequality, whereas negative percent change means reducing the inequality.
Abbreviations: CI; confidence interval

indicators, we need to evaluate inequality carefully, using broad indicators.

Another strength of our study was the large sample size for general applicability, representing the total Japanese population with a small baseline (2007) difference between intervention and comparison groups. Because this study is based on repeated cross sections instead of longitudinal data, changes to one individual could not be specified. Longitudinal studies, however, have the problem that disadvantaged people are likely to leave the study.[54] In this study, all respondents with characteristics of disadvantage could be included; this study design may thus complement longitudinal studies.

There are possible limitations to this study. First, as the information was self-reported, the study might not be free from biases, especially misclassification bias.[55] As this questionnaire was not designed for evaluation of the intervention, several modalities might be included in cancer screening. However, this would not change the DID results as the intervention only affected Pap smear and mammography testing. Second, our analysis could not distinguish whether the testing was being performed for screening or diagnostic purposes. Furthermore, although both physicians' behavior and people's knowledge and attitudes toward preventive care are important determinants of FCS attendance,[29] we could not include them because no data were collected in the survey. Third, some Japanese municipalities already deliver free FCS services to all eligible residents: 6.6% for CCS and 5.9% for BCS in January 2009.[4] This may lead to underestimation of the intervention effect. Fourth, average cost per uptake was calculated without considering switching costs. Because around 20–25% of the invitees used the vouchers in 2009 according to the government report[2] and uptake was estimated to be around 10–15% in this study, it is estimated that as a result of the intervention, around 10% of the invitees switched from their past practice (*e.g.*, workplace-based FCS) to using vouchers in their community with associated opportunity costs. Although opportunity costs for switching FCS attendance (*e.g.*, absence from work to attend FCS in the community in contrast to workplace-based FCS) were not available, the switch of financial source, which may lead to overestimation on the results of average cost per uptake, should be taken into account.

In conclusion, our results suggest that removal of out-of-pocket costs could potentially make a substantial contribution to FCS uptake and reduction of inequalities in BCS delivery due to household income inequality but may not be cost-saving. Careful and thoughtful consideration of the feasibility of continuing the intervention policy in terms of benefits and costs is required. This consideration should take account of the equity perspective as well as medical and economic factors. This study adds to a growing body of literature showing that we may need to invest extra efforts in reducing inequalities in cancer screening uptake.[56] In addition to uptake levels and average cost per uptake, policymakers should carefully consider the role of inequalities in the design of screening programs, to ensure that screening attendance pathways are closely monitored from an equity perspective.[57] Judgment as to whether a particular distribution of health is just, fair or socially acceptable may guide the interpretation of the data. Policymakers and researchers must therefore pay more attention to the normative choices inherent in measurement on which they base their evaluations of current and future health policies for remedying health inequalities.[35] Although the cost-removal intervention appears to have been successful in improving overall uptake for FCS during the first year of implementation, it is essential to continue monitoring attendance rates, average cost per uptake and socioeconomic inequality for FCS as the system matures.

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画像診断の進歩とその評価
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画像診断の進歩とその評価 ー低線量 CT 検診の場合ー

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Evaluation of diagnostic imaging - low dose CT for lung cancer -

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Abstract : It is difficult to evaluate whether to have to recommend a new modality as a periodical screening program, although increasing with the power of detection of tiny tumor by improving of diagnostic imaging. The randomized-controlled trial which to evaluate the efficacy of cancer screening as most importance approach, is necessary for the long period and every tens of thousands of participants. National Lung Screening Trial to evaluate low dose CT screening for lung cancer demonstrated 20% reduction of lung cancer mortality according to the study protocol. There is, however, no movement to recommend low dose CT screening as a national screening program for lung cancer, since 27 percent of high diagnostic workup rate and high fatality of biopsy cases. It is necessary to plan epidemiological study to evaluate a new promising modality as possible as an early stage, because there is unequal between the diagnostic modality and medical evaluation for cancer screening.
Key words : RCT, Cancer screening, LDCT

1. はじめに

がんの早期発見法の進歩は著しく，あらゆる臓器で，小型の腫瘍が発見されるようになってきている．しかしそういった早期発見法による定期検査によって発見されるがんの多くは進行速度が遅いものが多く（length biased sampling），これらは死に直結しないが，死に直結するような進行速度の速いがんは，定期検査では見つかりにくく，中間期癌の形で発生しうる（Fig.1）．このため，がんの早期発見法が当該がんの死亡リスク（受診者集団の死亡率）を軽減させ

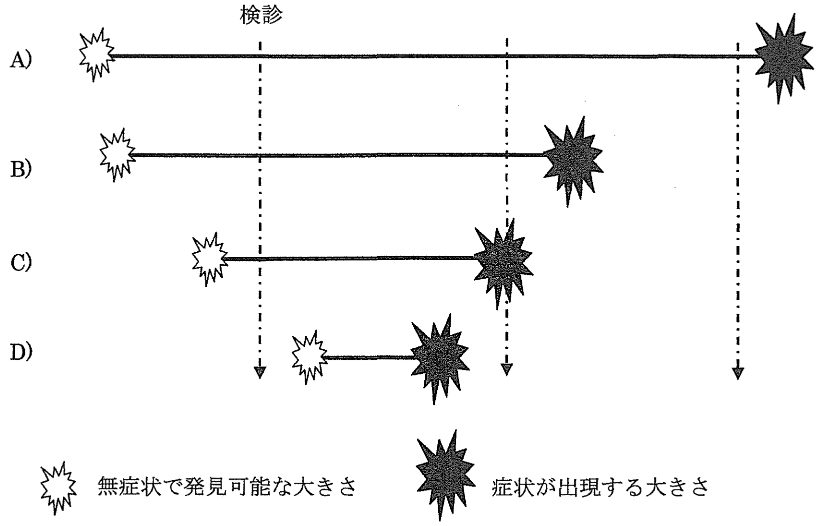


Fig.1　レングス・バイアス
定期的検診が行われた場合，A）では，3回の検診の機会いずれも早期で発見可能．B）では2回の検診の機会で早期発見可能．C）では早期発見可能なのは1回のみ．D）では定期検診による発見自体困難で中間期がんとして診断される．このように進行速度の遅いがん（＝予後のよいがん）が検診では発見されやすい．

るかどうかは，微小癌の発見率等では推定できるものではなく，受診者集団全体を追跡する大規模疫学研究以外に証明の方法がない．その疫学研究において，もっともエビデンスレベルが高いとされるランダム化比較試験の実施については，古くは70年代に行われた肺癌検診や乳癌検診の評価に始まり，約40年の歴史がある．しかし治療に関するランダム化比較試験と異なり，サンプルサイズが数千から数万に至り，研究期間が10年から15年と長きにわたることなどから容易に行い得ない．また治療と異なり対象者が健常者であり必ずしも検診を希望していないことから，リクルートやコンプライアンス，コンタミネーションなど様々な問題をはらんでおり，そのデザインが適切であったかどうかの評価は容易ではない．

2．肺癌検診でのランダム化比較試験その1（Mayo Lung Project）

肺癌検診の評価としては，70年代にNCI主導の4つのランダム化比較試験が行われたが，そのうち最大の規模であるMayo Lung ProjectがX線検査を用いた肺癌検診の直接的な証拠として重要視されてきた．1971年に開始されたこの研究では45歳以上の喫煙男性9,221名を4ヶ月検診群と対照群に割り付け，4ヶ月検診群には年3回の単純X線と喀痰細胞診を提供し，対照群には年1回の同じ検査を推奨するだけにとどめ，6年間の検診相を経た後に5年の追跡を行う予定であった[1]．1983年7月の時点で両群間の累積肺癌死亡率に差は認められず，胸部X線を中心に据えた肺癌検診は効果がないという結論になった．しかしこの研究では4ヶ月検診群に割り当てられた受診者のコンプライアンスが低いとか対照群が検診を受診していた（コンタミネーション）などの実施上の問題に加えて，研究群が対照群に比べて46例罹患が多い（研究群206例，対照群160例）という結果（Table 1）から胸部単純X線検査による検診では，「死亡率減少効果がなく，不利益として過剰診断が22%発生する」という過剰診断説が提唱されてきた[2].

Table 1　Mayo Lung Projectの肺癌罹患の状況（文献[1]より作成）

	研究群	対照群
検診発見	**90**	
胸部X線	66	
喀痰細胞診	18	
双方発見	6	
検診外発見	**116**	**160**
胸部X線*	43	48
症状	73	112
計	**206**	**160**

*；検診以外で撮影された胸部X線を示す．研究群においても年3回の研究の枠内の検査以外に更に胸部X線を受診しているものが少なくなかったことを示している．

3．肺癌検診でのランダム化比較試験その2（PLCO研究）

2011年に報告されたPLCO研究（Prostate, Lung, Colorectal, Ovarian screening trial）は，1993年から全米で行われた4つの臓器のがん検診（PSAを用いた前立腺癌，胸部単純X線を用いた肺癌，S状結腸鏡を用いた大腸癌，CA125を用いた卵巣癌検診）を同時に評価した大規模RCTである．肺癌検診の評価としては，Mayo Lung Projectでの過剰診断説を打破するために，追跡期間を10年に設定し，また10%前後の小さな死亡率減少効果を検出できるようにサンプルサイズも約15万人として実施された[3]．米国在住の55～74歳の男女（喫煙を問わない）を1993-2001年に登録し，年齢・性別でランダム化した．154,901人が登録され，年1回（計4回）の胸部単純X線を提供する介入群と非介入群に割り付け，検診相終了後10年間追跡した（Fig.2）．その結果試験終了時の研究群の肺癌死亡相対危険度は0.99（95%信頼区間0.98-1.12）であり，胸部単純X線を用いた肺癌検診は効果がないという結論であった．しかし論文上の累積死亡率の図表をみると，研究開始後5年目の時点で最大11%の死亡率減少効果が示されており，それが11年目で消失したという結果であった（Fig.3）．無検診のまま10年追跡するのではなく検診を継続していた場合に，より効果が開大した可能性を否定できない．奇しくも本研究では過剰診断は2～6%程度と考えられ，Mayo Lung Projectとは全く異なる結果となった．現在の単純X線と70年代のX線の画像の質から考えると，PLCOの方がより早期の病変を検出できたはずであり，過剰診断は多くなるはずである．この矛盾した結果から考えられることは，Mayo Lung projectの割り付けに問題があり，研究群が肺癌リスクの高い集団になってしまった可能性が示唆される．

4．肺癌検診でのランダム化比較試験その3（NLST）

NLST（National Lung Screening Trial）は，年1回の低線量CTの有効性評価を目的として2002年8月から行われた多施設共同のRCTである．対象者は少なくとも30 pack-yearの喫煙歴を有する男女とし，53,454例が登録され，研

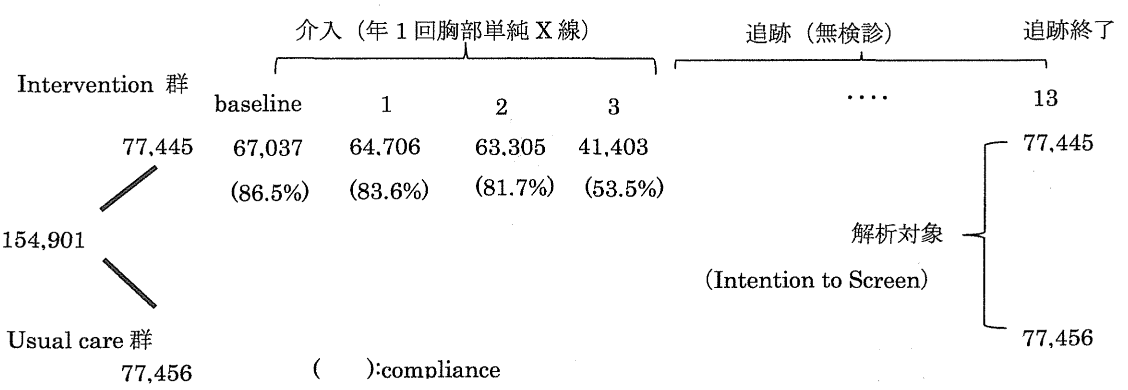
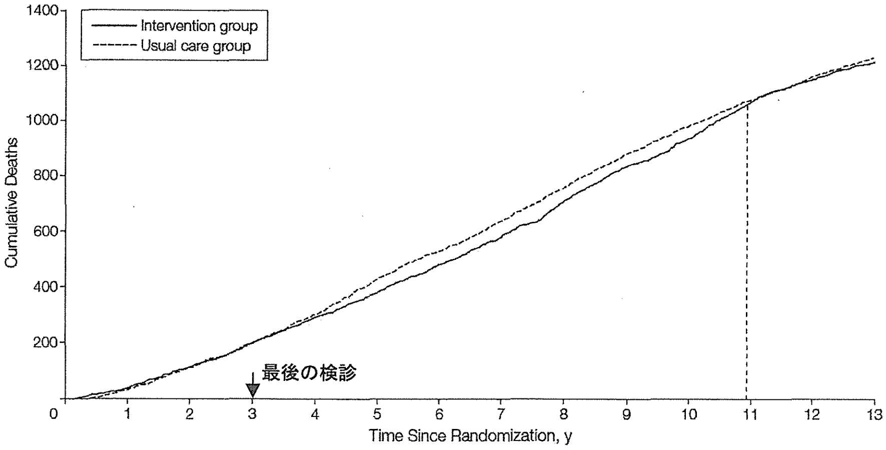


Fig.2　PLCOの肺癌検診の実施スケジュール（文献[3]より作図）
3年目の介入については，非喫煙者は原則中止とした．



肺癌死亡率	Intervention	46.6	73.4	85.1	95.5	99.3	105.5	110.2	118.5	125.0	127.5	135.5	138.1	140.4
	Usual care	38.8	72.0	86.0	98.4	111.9	115.9	121.1	126.9	131.9	134.4	136.4	139.7	142.5
死亡率減少効果		-20%	-2%	1%	3%	**11%**	**9%**	**9%**	7%	5%	5%	1%	1%	2%

Fig.3 PLCO の累積肺癌死亡数の推移（文献[3]より修正して引用）
検診が終了してから２年目において死亡率は 11% 減少したが徐々にその差は縮小し，最後の検診から約８年で差が消失した．

究群と対照群に無作為に割り付けられた．両群には年１回計３回の検診（研究群には低線量 CT，対照群には胸部単純 X 線）が提供された[4]．研究群については，4 mm 以上の肺結節およびリンパ節腫脹や胸水を“Positive”と判定する取り決めがなされた．3 年目の検診で大きさが変わらない結節は 4 mm 以上であっても“Positive”とは判定しないこととされた．検診相の後，約 5 年の追跡期間で研究群が対照群に比べて 20.0（95% 信頼区間：6.8-26.7，p＝0.004）％の肺癌死亡率減少効果があることが示された．研究群の全死因死亡者数は対照群に比べて 123 例少なく，この差は肺癌死亡の差（87 例）でほぼ説明できるものであり，まさにがん検診の受診により当該がんの死亡が減少し，ひいては全死因死亡が減少することが示された（がん検診により当該がんの死亡率は減少したとしても，結局は何らかの理由で死亡するので，全死因死亡は減少しない vs 全死因が減少しないのでは意味がない，という論争が長く疫学研究者の間に行われてきた）．この研究は，計画の段階で 20% の死亡率減少効果を想定してサンプルサイズ等を計算したものであるが，それがぴったりあったという点で，高く評価されるべき研究結果である．しかし問題は要精検率の高さと精密検査・治療に関する偶発症の多さである．報告された要精検率は，初年度・2 年目とも約 27% と過剰に高く，実に 4 人に 1 人以上が精密検査を要するという有様であった（Table 2）．また精密検査や治療に伴う重篤な偶発症率は極めて高く，精密検査を要し肺癌が確定した研究群 649 例中 10 例（1.5%）が検査後 60 日以内に死亡したと報告している（Table 3）．この死亡の中には検査や治療関連死以外のもの（原病死や他死因）が含まれているにせよ，あまりにも精密検査によるリスクが高いという印象を与えるものであった．このようなことから，国際肺癌学会（IASLC）をはじめとした団体は，CT 検診を未だ研究段階にあるものとして位置づけ，National screening program として採用する動きはない．

Table 2 NLST の検診結果（文献[4]より引用）

	介入（LDCT）群				対照（単純 X 線）群			
	受診者数	要精検率（%）	臨床的問題症例率（%）*	精検不要率（%）	受診者数	要精検率（%）	臨床的問題症例率（%）*	精検不要率（%）
初回	26,309	27.3	10.2	62.4	26,035	9.2	3.0	87.8
2 回目	24,715	27.9	6.1	65.9	24,089	6.2	1.8	92.1
3 回目	24,102	16.8	5.8	77.3	22,346	5.0	1.5	93.4

*；肺癌を疑わないが臨床的には follow up，精密検査，治療などが必要な症例の割合

Table 3 NLST の肺癌確定例の診断行為による偶発症（文献[4]より引用）

	介入（LDCT）群					対照（単純 X 線）群				
	外科的生検	気管支鏡	針生検	侵襲的診断行わず	計	外科的生検	気管支鏡	針生検	侵襲的診断行わず	計
精検総数	509	76	33	31	649	189	46	29	15	279
偶発症なし	344	69	26	26	465	130	42	28	14	214
重篤な偶発症	71	2	0	2	75	22	1	0	1	24
60日以内死亡	5（1.0%）	4（5.3%）	1	0	10（1.5%）	4（2.1%）	5（10.9%）	1	1	11（3.9%）

5. まとめ

このように，がん検診の評価方法としてのランダム化比較試験は，大規模かつ長期化するものである．多額の研究費をかけて長期間行った上に得られた結果には様々なバイアスが混入している可能性があり，結果の解釈は容易ではない．単一の試験で得られた結果が同時に報告された他国の結果と相反する場合（PSA を用いた前立腺癌検診でのERSPC[5]とPLCO[6]の結果の相違）もあり，何が真実であるのか？広く普及を図るよう推奨すべきか？を判断することも容易ではない．

近年これを嫌って，モデル分析で済まそうという試みは見られるが，モデル分析の場合，必要なパラメータの信頼性が問題になる．すなわち，単一の研究で得られたパラメータのみを使う場合であっても，その研究の質が担保されているかどうかが問われるし，複数の研究で得られたパラメータを用いた場合は，“いいとこ取り”になっていないかの吟味が要求される．またモデルが正しいかどうかの検証は容易ではなく，モデルの“癖”により同じパラメータを用いて結果が異なる可能性もある．

結局現時点では，質のよい大規模疫学研究を行う以外に，がん検診の評価は実施し得ない．医療機器の進歩は著しいが，その進歩に対して評価はあまりにも時間がかかりすぎる．検診目的の利用を想定する場合は，早い時期に疫学研究を開始するスケジュールを調整しなければいけない．

文　献

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[3] MM Oken, WG Hocking PA Kvale, GL Andriole, SS Buys, et al.: Screening by Chest Radiograph and Lung Cancer Mortality. The Prostate, Lung Colorectal, and Ovarian (PLCO) Randomized Trial, JAMA, 306(17), 1865-1873, 2011.

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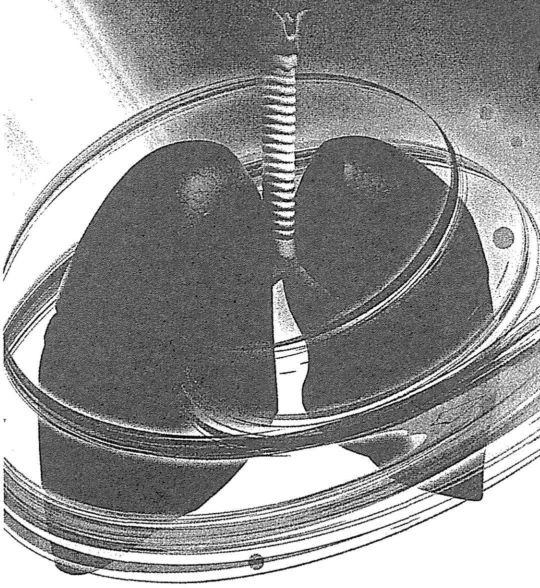
特集

肺がんCT検診を巡る国内外の動向と現状

―低線量CT検診の普及に向けて―



企画協力：花井耕造　国立がん研究センター東病院放射線部技師長

低線量CT検診の有効性を評価する米国における大規模RCT（NLSTやPLCO）の結果が昨年までに報告され，肺がんCT検診の有効性が証明されたことが大きなニュースとなりました。一方，3.11後のわが国では，医療被ばくに対しても国民からの厳しい眼が注がれています。今回のRCTの結果についても，低線量・低被ばくの観点から，慎重に対応することが求められるでしょう。そこで，これら大規模RCTの結果の解説と評価，そして，わが国における低線量CT検診の普及に向けた課題等をご報告いただき，議論と行動のきっかけとなることを願う小特集を企画しました。本特集が，低線量CT検診の理解と普及に向けた一助となることを期待します。

1．米国大規模RCT：PLCOおよびNLSTの結果についての考察

――肺がんCT検診の有効性を証明

中山　富雄　大阪府立成人病センターがん予防情報センター疫学予防課

肺がんは世界の大半の国でがん死因の第一位を占めることから，その対策の要求は大きいものの，従来の胸部単純X線撮影による早期発見は必ずしも容易ではなかった。低線量CTを用いた肺がん検診は，従来の単純X線で指摘不能な高分化腺癌を容易に高率に発見しうることから，その効果を大いに期待され，国内でも人間ドックを中心に普及している（注：ただし，国内の人間ドックで行われている“CT検診”の過半数は，低線量撮影ではないことも事実である[1)]）。

しかし，一般的に定期検査によって発見されるがんの多くは進行速度が遅く，死に直結しないものが多い（length biased sampling）。一方，死に直結するような進行速度の速いがんは，定期検査では見つかりにくく，検診間発見がんの形で発生しうる。このため，がんの早期発見法が当該がんの死亡リスク（受診者集団のがん死亡率）を軽減させるかどうかは，がんの発見率や生存率で推定できるものではなく，受診者集団全体を追跡する大規模疫学研究以外に証明の方法がない。

がん検診の効果を評価する疫学研究のうち，最もエビデンスレベルが高いとされるランダム化比較試験（RCT）については，1970年代から行われ，約40年の歴史があるが，サンプルサイズが数千から数万を要し，研究期間が10～15年と長きにわたることなどから，容易に行うことはできない。対象者のリクルートやコンプライアンス，コンタミネーションなどさまざまな問題をはらんでおり，そのデザインが適切であったかどうかの評価も容易ではない。ここでは肺がん検診の有効性評価の歴史について概説する。

胸部単純X線検診の評価

1970年代には，肺がんの高リスク群

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表1　MLP (Mayo Lung Project) の肺がん罹患の状況
(参考文献4) より作成)

	検診群	対照群
検診発見	90	
胸部X線	66	
喀痰細胞診	18	
双方発見	6	
検診外発見	116	160
胸部X線*	43	48
症状	73	112
計	206	160

*検診以外で撮影された胸部X線を示す。研究群においても年3回の研究の枠内の検査以外に，さらに胸部X線を受診しているものが少なくなかったことを示している。

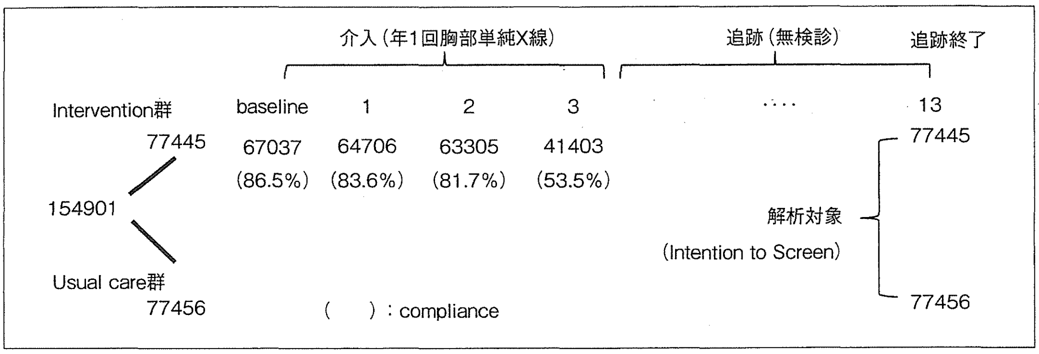


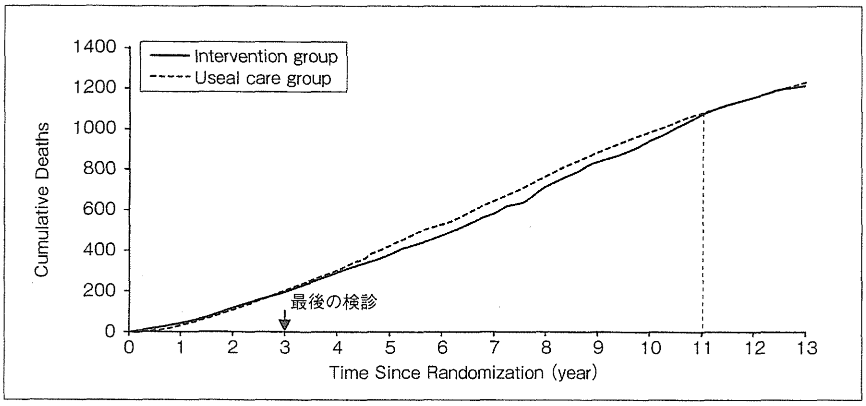
図1　PLCOの肺がん検診の実施スケジュール
3年目の介入については、非喫煙者は原則中止とした。
(参考文献3) より作成)

である喫煙者に対しては，定期的に胸部単純X線検査を提供することが，Mayo Clinicなどの米国の専門医療機関ではルーチンで行われていた。当時，喀痰細胞診が単純X線検査で指摘し得ない肺門部早期肺がんを発見できることが明らかになり，その上乗せ効果を評価することを主な目的として，4つのランダム化比較試験が米国を中心に行われた。その結果はいずれも，検診群の肺がん死亡率減少を示すことができなかったが，最大規模で行われたMLP (Mayo Lung Project) は，年3回検診と無検診 (実際は対照群の7割が検診を年1回受診していた) を比較した研究の結果の解釈が長く議論の的となった。すなわち，検診群と対照群の肺がん死亡率は差がなかったものの，両群の肺がん罹患数を比べると，検診群が対照群に比べて46例罹患が多かった (検診群206例，対照群160例)[2)] (表1)。このことから胸部単純X線検査による検診では，「死亡率減少効果がなく，不利益として過剰診断が22%発生する」という，過剰診断説が提唱されてきた[3)]。

しかし，胸部単純X線検診レベルでこれだけ多くの過剰診断が発生するのはおかしいのではないか？ 割り付けに問題があったのではないか？ という論争を招いた。このことを受けて，1993年から全米で大規模ランダム化比較試験PLCO研究 (Prostate, Lung, Colorectal, Ovarian screening trial) が開始された。この研究は，当時有効性の検証が未解決であった4つの臓器のがん検診手法を同時に評価したものである。肺がんについては大幅にサンプルサイズを拡大し，無検診での追跡期間を10年としてデザインされた[4)]。対象者は喫煙者に限定せず，非喫煙者も多く含んだことから，日本の肺がん検診の受診者とあまり差のない構成になっている。15万4901人を年1回 (計4回) の胸部単純X線を提供する介入群と非介入群に割り付け，検診相終了後10年間追跡した (図1)。

その結果，試験終了時の検診群の肺がん死亡相対危険度は0.99 (95%信頼区間：0.98～1.12) であり，胸部単純X線を用いた肺がん検診は効果がないという結論であった[4)]。しかし，論文上の累積死亡率の図表を見ると，研究開始後5年目の時点で最大11%の死亡率減少効果が示されており，それが研究開始後11年目 (検診終了後8年) で消失したという結果であった (図2)。

肺がんは，加齢により罹患リスクが急激に上がる疾患であり，無検診の追跡



Time Since Randomization		1年目	2年目	3年目	4年目	5年目	6年目	7年目	8年目	9年目	10年目	11年目	12年目	13年目
肺がん死亡率	Intervention	46.6	73.4	85.1	95.5	99.3	105.5	110.2	118.5	125.0	127.5	135.5	138.1	140.4
	Usual care	38.8	72.0	86.0	98.4	111.9	115.9	121.1	126.9	131.9	134.4	136.4	139.7	142.5
死亡率減少効果		−20%	−2%	1%	3%	11%	9%	9%	7%	5%	5%	1%	1%	2%

図2 PLCOの累積肺がん死亡数の推移
検診が終了してから2年目において死亡率は11％減少したが，徐々にその差は縮小し，最後の検診から約8年で差が消失した。
（参考文献4）より修正して引用）

表2 NLSTの検診結果（参考文献5）より引用転載）

	研究（LDCT）群				対照（単純X線）群			
	受診者数	要精検率（%）	臨床的問題症例率（%）*	精検不要率（%）	受診者数	要精検率（%）	臨床的問題症例率（%）*	精検不要率（%）
初 回	26309	27.3	10.2	62.4	26035	9.2	3.0	87.8
2回目	24715	27.9	6.1	65.9	24089	6.2	1.8	92.1
3回目	24102	16.8	5.8	77.3	22346	5.0	1.5	93.4

＊肺がんを疑わないが，臨床的にはfollow up，精密検査，治療などが必要な症例の割合

相に発生した肺がんの影響が，短い検診相の効果を凌駕したのではないかと考えられる。奇しくも，本研究では過剰診断は2〜5%程度と考えられ，70年代の画像機器で行われたMLPに比べてはるかに小さかった。70年代の研究結果に引きずられて立案した研究計画自体に問題があり，結果をゆがめてしまった可能性が示唆される。

低線量肺がんCT検診の評価

2010年の秋に報告されたNLST（National Lung Screening Trial）は，年1回の低線量CTの有効性評価を目的として，2002年8月から行われた多施設共同のRCTである。対象者は少なくとも30pack-yearの喫煙歴を有する男女とし，5万3454例が登録され，研究群と対照群に無作為に割り付けられた。両群には年1回，計3回の検診（研究群には低線量CT，対照群には胸部単純X線）が提供された[5]。研究群については，4mm以上の肺結節およびリンパ節腫脹や胸水を“陽性”と判定する取り決めがなされた。3年目の検診で大きさが変わらない結節は，4mm以上であっても“陽性”とは判定しないことも取り決められた。

検診相の後，約5年の追跡期間で研究群が対照群に比べて20.0%（95%信頼区間：6.8〜26.7，p＝0.004）の肺がん死亡率減少効果があることが示された。研究群の全死因死亡者数は対照群に比べて123例少なく，この差は肺がん死亡の差（87例）でほぼ説明できるものであり，まさにがん検診の受診により当該がんの死亡が減少し，ひいては全死因死亡が減少することが示された（がん検診により当該がんの死亡率は減少したとしても，結局は何らかの理由で死亡するので，全死因死亡は減少しない vs. 全死因が減少しないのでは意味がない，という論争が，長く疫学研究者の間に行われてきた）。

この研究は，計画の段階で20%の死亡率減少効果を想定してサンプルサイズ等を計算したものであるが，予想通りに観察されたという点で，高く評価されるべき研究結果である。しかし問題は，要精検率の高さと精密検査・治療に関する偶発症の多さである。報告された要精検率は，初年度・2年目ともに約27%と過剰に高く，実に4人に1人以上が精密検査を要するという有様であった（**表2**）。研究に関与した放射線科医たちが，研究計画立案時点ではまだ低線量CT検

表3 NLSTの肺がん確定例の診断行為による偶発症（参考文献5）より引用転載）

	研究（LDCT）群					対照（単純X線）群				
	外科的生検	気管支鏡	針生検	侵襲的診断行わず	計	外科的生検	気管支鏡	針生検	侵襲的診断行わず	計
精検総数	509	76	33	31	649	189	46	29	15	279
偶発症なし	344	69	26	26	465	130	42	28	14	214
重篤な偶発症	71	2	0	2	75	22	1	0	1	24
60日以内死亡	5 (1.0%)	4 (5.3%)	1	0	10 (1.5%)	4 (2.1%)	5 (10.9%)	1	1	11 (3.9%)

診の経験が乏しいことから，まずは微小肺結節を残さず把握したいという欲求から，4mm以上の結節という陽性の定義にしてしまったのではないかと想像される。他のプロトコールでは，おおむね5mm以上とかさまざまな条件を追加して，要精検の定義を狭くしているが，20数%という要精検率ではとても一般化できない（厚生労働省の指針によれば，各種がん検診の指標値はそれぞれ数%台未満である）。

また，精密検査や治療に伴う重篤な偶発症率として報告された成績はきわめて高く，精密検査を要し，肺がんが確定した研究群649例中10例（1.5%）が，検査後60日以内に死亡したと報告している（表3）。この死亡の中には，検査や治療関連死以外のもの（原病死や他死因）が含まれているにせよ，あまりにも精密検査によるリスクが高いという印象を与えるものであった。

このようなことから，国際肺がん学会（IASLC）をはじめとした各種団体は，CT検診をいまだ研究段階にあるものとして位置づけており，national screening programとして採用する動きはない。

◎

肺がん検診の有効性を評価する2つのランダム化比較試験について概説した。いずれの研究も完璧にデザインされたというものではなく，いまだに問題を抱えている。せっかく肺がん死亡率減少効果を計画通りに示したNLSTにおいても，その過剰に高い要精検率では容易に一般化できないという印象を与えた。現在，日本CT検診学会の全国調査では，低線量CT検診実施施設での要精検率は6%程度に低下しており[6]，その状況であれば一般化も可能と考えられるものの，前述した日本人間ドック学会の調査によれば，撮影条件さえも低線量になっていない施設が一方では多い[1]ことも問題である。この2つの学会における調査の乖離は，各学会の会員が共通していないことによる。学会ベースでのガイドライン等はあくまで会員に限定して利用されることから，学会の壁を越えたガイドラインの構築が必要である。

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原著

子宮頸がん検診の無料クーポン券配布および未受診者への受診再勧奨の効果：コール・リコール制度の試み

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