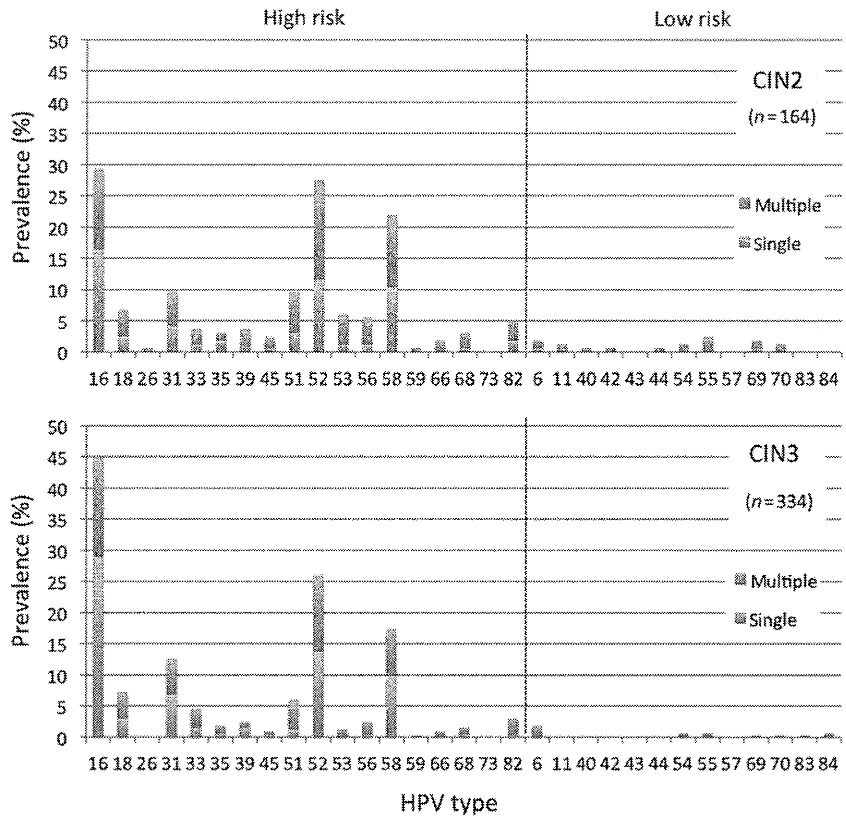


**Figure 1.** Human papillomavirus (HPV) type distribution in cervical intraepithelial neoplasia (CIN) Grade 2/3 in Japanese women. The proportions of single and multiple infections are presented for individual types. HPV types are grouped as either high- or low-risk based on the risk classification of Munoz et al. (2), except that HPV26 and HPV53 are included in the high-risk group based on phylogenetic classification of the L1 nucleotide sequences.

the 149 ICC cases (87.9%). Table 1 and Figure 1 show the prevalence and genotype distribution of both high- and low-risk HPVs in the CIN2/3 cases that were enrolled in this study. In CIN2 and CIN3, three genotypes, HPV16, HPV52 and HPV58, were predominantly detected among 31 HPV types examined. The proportion of these HPV types in each histological stage was as follows: HPV16 (29.3%), HPV52 (27.4%) and HPV58 (22.0%) in CIN2; HPV16 (44.9%), HPV52 (26.0%) and HPV58 (17.4%) in CIN3. Low-risk HPVs were detected in 18 cases (11.0%) in CIN2 and 14 cases (4.2%) in CIN3, all with other high-risk HPVs except for one case of single-positive HPV6 in CIN2 and one case of single-positive HPV69 in CIN2. The proportion of low-risk HPV infections was significantly lower in CIN3 than in CIN2 ($P = 0.007$, $\chi^2$ test).

In accordance with the distribution patterns observed with CIN2/3 lesions, HPV16 (47.7%) was most frequently detected in ICC, whereas the second common type was HPV18 (23.5%), followed by HPV52 (8.7%) (Table 2). Among the ICC cases, the detection rate of HPV DNA was relatively low in adenocarcinoma (71.4%) compared with squamous cell carcinoma (SCC) (97.8%), and type distributions of high-risk HPVs were apparently different between the two histological types (Fig. 2), as previously reported (14). Although HPV16 (60.4%) was the most common type in SCC, followed by HPV52 (12.1%) and HPV18 (11.0%), HPV18 (41.1%) was most frequently detected in adenocarcinoma, followed by HPV16 (28.6%) and HPV51 (5.4%).

### Prevalence Ratio

To evaluate the risk of CIN progression attributable to individual high-risk HPVs, the prevalence ratio (PR) of each high-risk HPV was calculated by comparing the incidence in CIN3 and CIN2. As shown in Table 1, HPV16 prevalence was significantly higher in CIN3 compared with CIN2 (PR = 1.62, 95% CI = 1.26–2.13). Conversely, HPV53 prevalence was negatively associated with progression from CIN2 to CIN3 (PR = 0.23, 95% CI = 0.06–0.69). CIN2/3 and SCC cases positive for HPV16 showed a trend towards younger age compared with HPV16-negative cases (Fig. 3). Indeed, statistical analysis, using a log-binomial model, of high-risk HPVs prevalence in CIN2 and CIN3 with age revealed significantly higher PR with decreasing age for HPV16 (PR/year = 1.03,

**Table 2.** HPV genotype distribution in ICC in Japanese women

| Type | ICC (*n* = 149) | % | SCC (*n* = 91) | % | Adc (*n* = 56) | % | PR (SCC vs. CIN3) (95% CI) | *P* (Wald test) |
|---|---|---|---|---|---|---|---|---|
| High risk | | | | | | | | |
| 16 | 71 | 47.7 | 55 | 60.4 | 16 | 28.6 | **1.55 (1.25–1.87)** | **0.000007**** |
| 18 | 35 | 23.5 | 10 | 11.0 | 23 | 41.1 | 1.62 (0.72–3.33) | 0.20 |
| 26 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | ND | |
| 31 | 3 | 2.0 | 3 | 3.3 | 0 | 0.0 | **0.23 (0.05–0.65)** | **0.017*** |
| 33 | 4 | 2.7 | 3 | 3.3 | 1 | 1.8 | 0.70 (0.15–2.22) | 0.59 |
| 35 | 2 | 1.3 | 2 | 2.2 | 0 | 0.0 | 1.69 (0.24–7.38) | 0.52 |
| 39 | 3 | 2.0 | 3 | 3.3 | 0 | 0.0 | 1.07 (0.20–4.14) | 0.93 |
| 45 | 1 | 0.7 | 1 | 1.1 | 0 | 0.0 | 0.98 (0.04–9.24) | 0.99 |
| 51 | 3 | 2.0 | 0 | 0.0 | 3 | 5.4 | ND | |
| 52 | 13 | 8.7 | 11 | 12.1 | 2 | 3.6 | **0.47 (0.24–0.82)** | **0.014*** |
| 53 | 1 | 0.7 | 0 | 0.0 | 0 | 0.0 | ND | |
| 56 | 3 | 2.0 | 2 | 2.2 | 1 | 1.8 | 0.93 (0.13–3.97) | 0.93 |
| 58 | 8 | 5.4 | 6 | 6.6 | 2 | 3.6 | **0.38 (0.15–0.80)** | **0.024*** |
| 59 | 1 | 0.7 | 0 | 0.0 | 1 | 1.8 | ND | |
| 66 | 2 | 1.3 | 1 | 1.1 | 1 | 1.8 | 0.57 (0.02–6.46) | 0.69 |
| 68 | 3 | 2.0 | 3 | 3.3 | 0 | 0.0 | 3.26 (0.67–13.0) | 0.11 |
| 73 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | ND | |
| 82 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | ND | |
| Low risk | | | | | | | | |
| 42 | 1 | 0.7 | 0 | 0.0 | 1 | 1.8 | | |
| 54 | 3 | 2.0 | 3 | 3.3 | 0 | 0.0 | | |
| Negative | 18 | 12.1 | 2 | 2.2 | 16 | 28.6 | | |
| Multiple | 21 | 14.1 | 13 | 14.3 | 7 | 12.5 | | |

Single and multiple infections combined.
$^{**}P < 0.001$; $^{*}P < 0.05$; ND, not determined. Statistically significant values are indicated in boldface.
One adenosquamous carcinoma (HPV18 positive) is included in Adc. One small cell carcinoma (HPV18 positive) and one undifferentiated carcinoma (HPV18/53 positive) included in SCC are excluded from SCC and Adc.
ICC, invasive cervical cancer; SCC, squamous cell carcinoma; Adc, adenocarcinoma; CIN3, cervical intraepithelial neoplasia Grade 3; PR, prevalence ratio; CI, confidence interval.

95% CI = 1.01–1.04, $P = 0.0009$) and for HPV68 (PR/year = 1.13, 95% CI = 1.03–1.27, $P = 0.021$). No significant association with age was observed for prevalence of other high-risk types (data not shown).

When the prevalence of high-risk types was analyzed between CIN3 and SCC, an excess of HPV16 was found in SCC compared with CIN3 (HPV16: PR = 1.55, 95% CI = 1.25–1.87) (Table 2). In contrast, the prevalence of HPV31, HPV52 and HPV58 was significantly decreased in SCC compared with CIN3.

### Multiple Infections

As shown in Figure 4A, multiple infections were detected in 38.4% of the CIN2 cases, 29.6% of the CIN3 cases and 14.1% of the ICC cases, showing a decreasing trend with severity of lesions, whereas the proportion of single infection increased from 57.9% in CIN2 to 73.8% in ICC. The number of detected HPV types significantly decreases as the lesion develops to ICC ($P = 0.0005$) and with age ($P = 1.3 \times 10^{-6}$). Among multiple infections, the proportion of HPV16 and/or HPV18 infections with other high-risk HPVs was 15.9% in CIN3, which was significantly higher than the 6.7% in ICC ($P = 0.009$), but not significantly different to the 12.2% in CIN2 ($P = 0.34$) (Fig. 4B). The proportion of HPV16 and/or HPV18 infections without other high-risk HPVs was significantly higher in CIN3 than in CIN2 ($P = 0.006$), and was higher still in ICC than in CIN3 ($P = 1.7 \times 10^{-8}$). In contrast, the proportion of high-risk HPV infections other than HPV16/18 was significantly lower in CIN3 than in CIN2 ($P = 0.010$), and was yet lower in ICC than in CIN3 ($P = 1.8 \times 10^{-9}$).

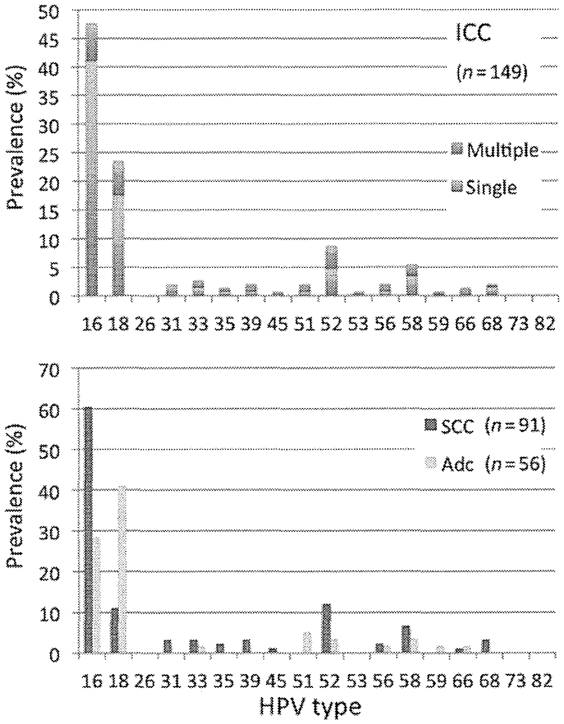


**Figure 2.** HPV type distribution in invasive cervical cancer (ICC) in Japanese women. The prevalence of single and multiple infections in ICC for individual types (upper panel). The type distribution in squamous cell carcinoma (SCC) and adenocarcinoma (Adc) (lower panel).

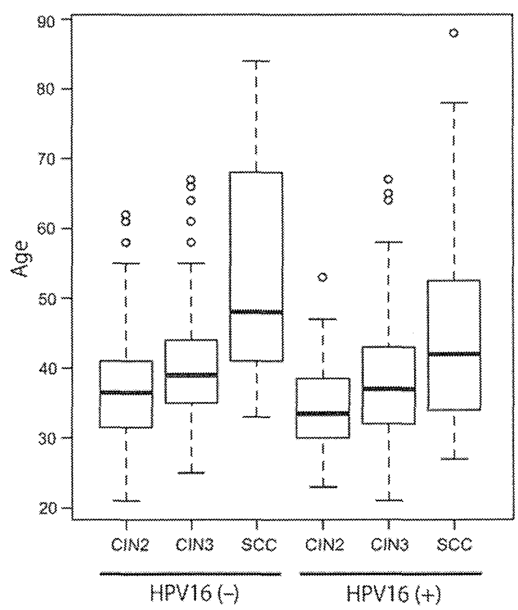


**Figure 3.** Association of age with HPV16 positivity in CIN2/3 and SCC.

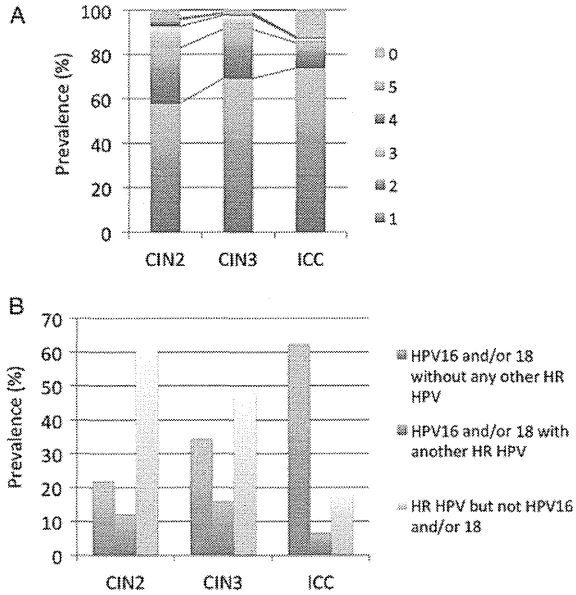


**Figure 4.** Multiple HPV infections in CIN2/3 and ICC in Japanese women. (A) The distribution of the number of HPV types detected for each histological grade. (B) The prevalence of HPV16 and/or 18 and other high-risk HPVs, alone or in mixed infections with HPV16 and/or 18, for each histological grade.

With regard to the three most frequent types detected in CIN2/3, the proportion of co-infections was as follows: in CIN2, HPV16/52 in 8 cases (4.9%), HPV16/58 in 4 cases (2.4%), and HPV52/58 in 8 cases (4.9%); in CIN3, HPV16/52 in 14 cases (4.2%), HPV16/58 in 9 cases (2.7%), and HPV52/58 in 8 cases (2.4%) (Fig. 5). Triple-infections were found in two cases of CIN2 and in one case of CIN3.

## DISCUSSION

Here we have presented the prevalence and type distribution of high-risk HPVs in cervical precancerous lesions and ICC in Japan using a validated genotyping method. A number of studies have so far been conducted to investigate the HPV type distribution in Japanese women (8–10, 15–19), but most of those studies depended on HPV typing performed at each hospital laboratory and only a limited number utilized a centralized external laboratory with quality assurance of its testing capability. Since our typing capability using the PGMY-lineblot assay has been consistently evaluated as proficient in the HPV DNA proficiency panel studies conducted annually by the WHO HPV laboratory network (20), the results obtained in this study provide the most recent and reliable pre-vaccination baseline data for Japanese HPV infection.

In a meta-analysis assembling HPV genotyping data from 984 ICC cases in Japan, the top three HPV types were HPV16 (44.8%), HPV18 (14.0%), and HPV52 (7.0%) (7). The

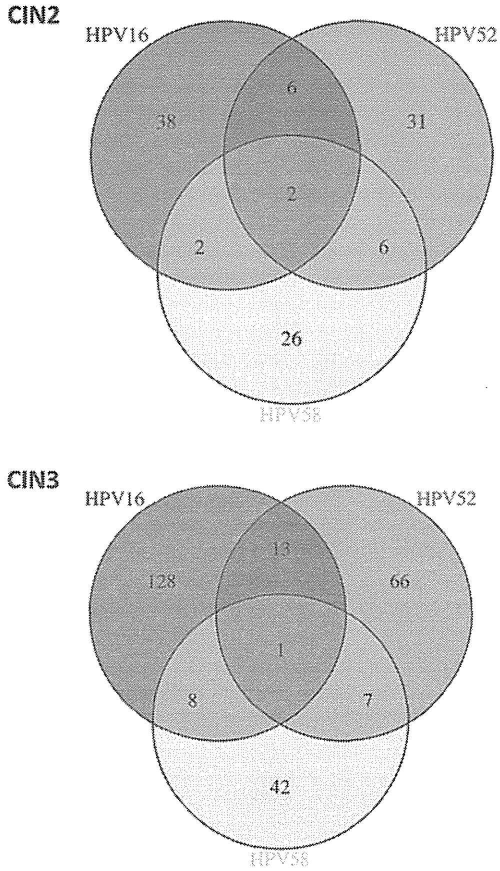


**Figure 5.** Venn diagram showing the overlap of HPV16/52/58 infections in CIN2 (A) and CIN3 (B). The number in circles indicates the number of subjects positive for HPV16 and/or HPV52 and/or HPV58.

observed distribution of high-risk HPVs in ICC reported in this study is almost similar, suggesting that the general trend for causative HPV types in ICC has not dramatically changed in Japan. The type distributions in SCC and adenocarcinoma found in this study are also similar to those reported in the previous meta-analysis (7), in which the top three most frequent HPV types were HPV16 (45.8%), HPV18 (10.8%) and HPV52 (7.4%) in SCC, and HPV18 (58.2%), HPV16 (31.3%) and HPV68 (4.5%) in adenocarcinoma. However, HPV68 was not detected in adenocarcinoma in this study.

Compared with the high HPV positivity in SCC (97.8%), the low HPV detection rate observed in adenocarcinoma (71.4%) is consistent with a recent study summarizing HPV genotyping data for cervical adenocarcinoma (21), which demonstrated that the positivity rate of HPV DNA in adenocarcinoma ranged from 65.6% (6) to 82.0% (22). The HPV-negative adenocarcinoma cases ($n = 16$) in this study were further examined by PCR targeting the HPV E6 gene, but again no HPV DNA was amplified from these samples (data not shown). The low detection rate of HPV DNA may be due to HPV integration into the host genome that disrupts the L1 and E6 genes used for HPV typing, improper sampling of endocervical cells, or degradation of cell samples containing low levels of HPV DNA. The low HPV positivity in cervical adenocarcinoma may also be attributed to the presence of inherently HPV-unrelated glandular lesions. In support of this notion, gastric-type adenocarcinoma, which exhibits a range of phenotypic gastric differentiation, has recently been proposed as another subtype of cervical adenocarcinoma and shown to be unrelated to HPV infection (23). Nevertheless, gastric-type adenocarcinoma was not found in the adenocarcinoma cases in this study.

The HPV type distribution in CIN2/3 in this study shows similar patterns to that previously reported by Onuki et al. (17), in which the top three most frequent types were HPV16 (24.1%), HPV52 (17.5%) and HPV58 (10.7%). Thus, the results in this study strongly support a major role for HPV16, HPV52 and HPV58 in causing CIN2/3 in Japanese women.

A recent prospective study followed Japanese women with low-grade cervical lesions and estimated the risk of disease progression associated with high-risk HPV infections (24). That study reported hazard ratios of individual high-risk types for progression to CIN3; 7 HPV types (HPV16, 18, 31, 33, 35, 52 and 58) showed a high risk of progression. Consistent with these findings, in our study HPV16 exhibited significantly higher PR in CIN3 compared with CIN2, suggesting a higher potential for progression from CIN2 to CIN3 than with other high-risk types. Faster progression of HPV16-infected lesions to CIN3 can also explain the observed association of younger age with the development of HPV16-positive CIN3. The high PR of HPV16 in SCC compared with CIN3 lends further support to the increased carcinogenicity of persistent HPV16 infection. In contrast, we found a low prevalence of HPV31, HPV52 and HPV58 in SCC compared with CIN3, which suggests a lower potential for progression to SCC than with HPV16 infection.

Multiple infections were more frequently detected in CIN2/3 in our results than in those reported by Onuki et al. (11.3% in CIN2/3) (17). This difference likely reflects the higher sensitivity of the PGMY-lineblot genotyping methodology to detect multiple infections, without inter-type PCR competition, as previously reported (25). Alternatively, the high prevalence of multiple infections might result from using cervical exfoliated cell instead of tissue sections containing CIN2/3 lesions. However, multiple infections with high-risk types have previously been reported in a study using tissue sections from cervical biopsies (26).

Caution should be taken regarding co-infections of HPV16/18 with other high-risk types, because currently available vaccines targeting HPV16/18 exhibit only limited cross protection against infections with other high-risk HPVs (3). We report a substantial proportion of HPV16/18 co-infections with other high-risk HPVs in CIN3 (Fig. 4B), a proportion that is significantly higher than that in ICC. Although a causative HPV type for CIN3 lesions is difficult to determine when co-infections are detected, the co-infection may still progress to ICC via the other high-risk types if HPV16/18 infections were prevented by vaccination. Of particular concern is the fact that HPV52 and HPV58 are commonly detected in East Asian countries and we report a significant number of co-infections between HPV52/58 and HPV16 in CIN2/3 in Japanese women (Fig. 5). Therefore, there is a possibility of an increase in the incidence of HPV52/58-positive ICC if HPV16/18 infections are prevented. Thus, careful monitoring of these genotypes in CIN2/3 lesions will be required after the widespread introduction of HPV vaccines into Japan and other East Asian countries in order to evaluate the overall efficacy of HPV vaccination.

## Acknowledgement

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## Conflict of interest statement

None declared.

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FORUM

# わが国の子宮頸がん罹患の実態
## ──子宮頸がん罹患は“若年化”しているのか？

齊藤英子／さいとうえいこ
国際医療福祉大学三田病院予防医学センター
青木大輔／あおきだいすけ
慶應義塾大学医学部産婦人科

最近，“わが国で子宮頸がん罹患が若年化している”という表現をしばしば耳にするが，その実態についてはあまり具体的に述べられていないので，実際のデータを紹介したい．国立がん研究センターがん情報サービスの公表している1975〜2010年の全国罹患推計値[1]をもとにグラフを作成した．

図1-Aはわが国における55〜84歳の子宮頸がん(浸潤がん)罹患率の推移を年代別にみたものである．いずれの年齢層においても減少傾向がみられた後，2000年代はほぼプラトーになっている．図1-Bは55〜84歳の上皮内がん罹患率の推移であり，2000年代後半に微増しているようにもみえるが，いずれの年代でも1975年以降大きな変動はない．

図2-Aは20〜54歳の浸潤がん罹患率の推移を示している．50〜54，45〜49，40〜44の年齢層では当初罹患率の減少を示したものの，2000年代から緩やかな増加を示している．35〜40，30〜34，25〜29歳では総じて緩やかな増加がみて取れる．図1-Aと図2-Aの比較から，罹患率はもともと55歳以上で高かったものが漸減し，2000年代になると30〜54歳の年代での罹患が55歳以上のそれに匹敵するようになった，と読み取れる．20歳代の罹患は30歳代以上のものの半分以下である．

図2-Bは20〜54歳の上皮内がん罹患率の推移である．この年代のすべてでほぼ全期間を通じて増加傾向がみられること，また2000年代後半から急激に罹患率が増加しているという特徴がみられる．この傾向が強いのは25〜44歳である．20〜24歳での上皮内がん罹患はそれほど多くはなく，2005年以降は50〜54歳のそれとほぼ重なっている．今日，上皮内がんの罹患が多いのは25〜44歳である．また，図2-Aと図2-Bとの比較より20〜54歳では上皮内がん罹患が大幅に増加しているにもかかわらず，浸潤がん罹患の増加は著しくないという乖離が読み取れる．

以上よりいえることは，“かつてわが国では子宮頸がん(浸潤がん)は55歳を超える年齢層に多かったが，その年代での罹患が減少した後に下げ止まっており，今日では30歳以上のすべての年齢において20〜30人/10万人程度の罹患がある”ということであり，罹患の若年化という単純なく

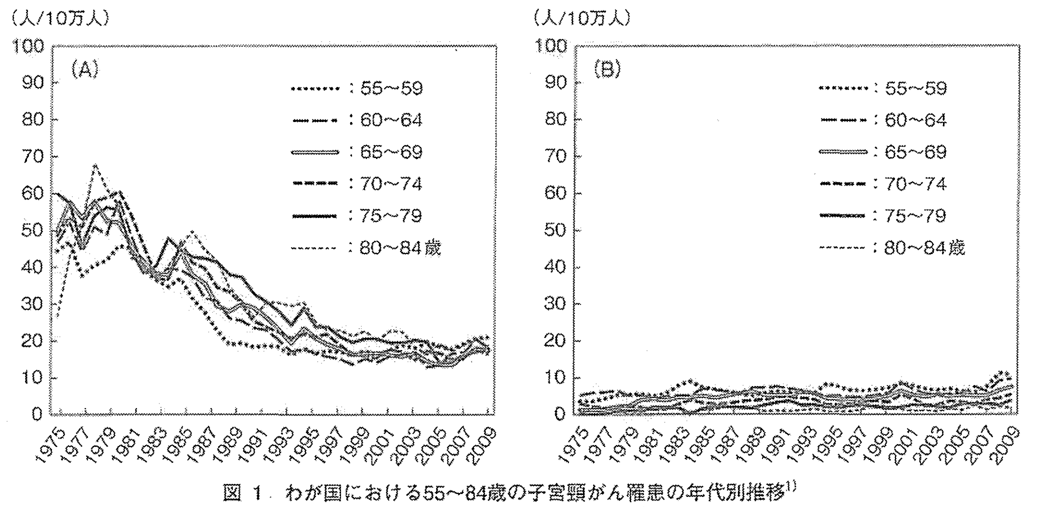


図1　わが国における55〜84歳の子宮頸がん罹患の年代別推移[1]
A：浸潤がん罹患率の推移(1975〜2010年)．
B：上皮内がん罹患率の推移(1975〜2010年)．

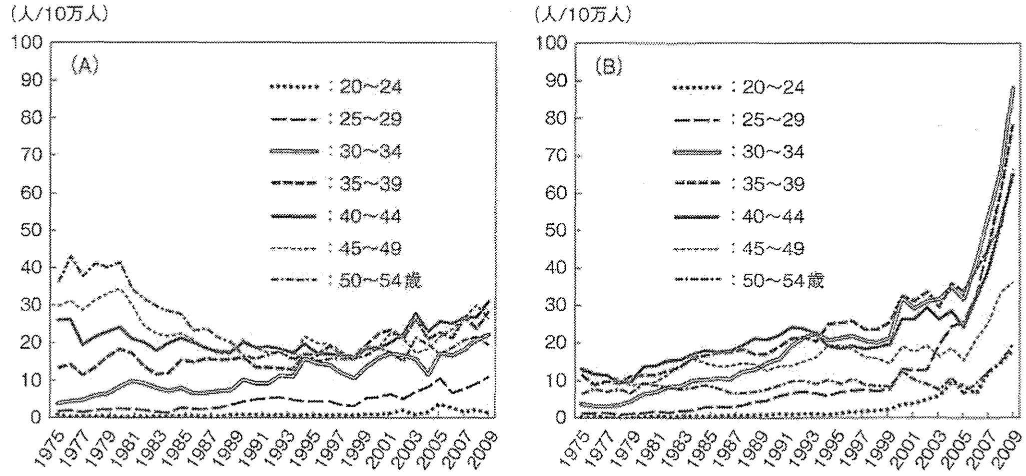


**図 2　わが国における20〜54歳の子宮頸がん罹患の年代別推移[1)]**
A：浸潤がん罹患率の推移(1975〜2010 年).
B：上皮内がん罹患率の推移(1975〜2010 年).

くりとはやや異なる印象を呈している.

これを共通認識としたうえで，現状を考察してみたい.

## がん検診の提供体制の影響

わが国で 30 歳以上を対象とした子宮頸がん検診は 1983 年から全国で実施され，2003 年からは 20 歳以上に対象が拡大された．2009 年からは 20 歳，25 歳，30 歳，35 歳，40 歳を対象とした子宮頸がん検診無料クーポン券の配布が行われ，新規受診者が増加したとみられている．こういったことを契機に，2000 年代に入って検診に 20〜40 歳代の新規受診者が参入したとすれば，この年代での一時的な上皮内がんおよび早期浸潤がんの増加が観察されている可能性がある．とすると，十分な検診曝露が続けば，この集団における浸潤がん罹患の減少がやがて観察されることになるであろう．実際，この年代での子宮頸がん検診の受診率は上昇しており，2010 年度の地域保健・健康増進事業報告による受診率は 20〜24 歳；24.6%，25〜29 歳；52.8%，30〜34 歳；59.4%，35〜39 歳；55.0%，40〜44 歳；67.4%，45〜49 歳：47.4%[2)]になっている．今後，検診受診率と罹患率の推移に注目すべきである.

## CIN 分類の導入

わが国では 1997 年ごろより CIN(cervical intraepithelial neoplasia；子宮頸部上皮内腫瘍)の概念が導入されはじめ，上皮内がん(carcinoma in situ：CIS)と高度異形成の両者が CIN3 に分類されるようになった．日本産科婦人科学会が編纂した子宮頸がん取扱い規約(第 3 版)によれば，2012 年以降は上皮内がんが子宮頸がんの進行期(0 期)として取り扱われなくなり，CIN という位置づけになる．この分類変更の過渡期である 2000 年代以降では CIN3 と病理診断されたもので，かつての分類での高度異形成であったものまでもが上皮内がんとして誤分類され，上皮内がん報告数の急激な増加に結びついている可能性も否めない．いずれにしても，今後は上皮内がんを子宮頸がんとして計上しないため，罹患の推移は浸潤がんで評価することになる．また，CIN3 についてもがんと区別して集計することが欧米ではすでに行われており，国際比較の観点からもわが国もそれに倣うべきであろう.

以上より，今後のわが国では子宮頸がん罹患に対しては浸潤がん罹患率を指標として評価を行うこととし，とくに 30〜54 歳を中心とした浸潤がんの罹患減少をめざした対策をとることが肝要である.

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RESEARCH ARTICLE

# What is the Most Effective Strategy for Improving the Cancer Screening Rate in Japan?

Hiroshi Sano[1*], Rei Goto[2], Chisato Hamashima[3]

## Abstract

**Background: Cancer screening rates in Japan are much lower than those in Western countries. This study evaluated the relationship between cancer screening rates and strategies used to improve screening rates, and determined which strategy is the most effective. Materials and Methods: All municipalities are responsible for conducting gastric, lung, colorectal, cervical, and breast cancer screenings in Japan. Of the 1,746 municipalities in total, 92-99% were included in the analyses for each cancer screening. Using national data in 2009, the correlations between cancer screening rates and strategies for improving screening rates of all municipalities, both large (populations of over 30,000) and small (populations of under 30,000), were determined. The strategies used were as follows: sending personal invitation letters, personal visits by community health workers, use of a clinical setting for screening, and free screening. Results: Of all four strategies used to improve cancer screening rates, sending personal invitation letters had the highest correlations with all screening rates, with the exception of breast cancer screening. The partial correlation coefficients linking this strategy with the screening rates in all municipalities were 0.28, 0.32, 0.30, and 0.26 for gastric, lung, colorectal, and cervical cancer screening, respectively. In large municipalities, the correlations between the number of examinees in a clinical setting and the screening rates were also relatively high, particularly for cervical cancer screening (r=0.41). Conclusions: Sending personal invitation letters appears to be particularly effective in improving cancer screening rates in all municipalities. All municipalities should implement a system that sends personal invitation letters for cancer screening. In large municipalities, increasing the availability of screening in a clinical setting is also effective in improving cancer screening rates.**

**Keywords:** Cancer screening - screening rate - strategy to increase participation- correlation - Japan

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## Introduction

Since population-based screening for cancer was introduced under the Health and Medical Service Act for the elderly in 1983, municipalities have been responsible for conducting cancer screenings in Japan. Screening programs for five kinds of cancers (gastric, lung, colorectal, cervical, and breast cancers) have become continuously conducted by all municipalities. However, cancer screening rates in Japan are much lower than those in Western countries and Korea, including examinations other than population-based screening that are conducted as part of a public policy to reduce mortality rates. While the screening rates for breast and cervical cancer in 2010 were 80.4% and 85.0%, respectively, in the United States, 70.9% and 67.9% in Korea, and 73.4% and 78.5%, in the United Kingdom, both screening rates were 24.3% in Japan (OECD, 2011; Suh et al., 2013).

To improve cancer screening rates, effective strategies that motivate people to be screened need to be successfully implemented. The U.S. Center for Disease Control and Prevention (CDC) conducted systematic reviews on the effectiveness of various interventions in increasing the screening rates for breast, cervical, and colorectal cancers, and published guidelines based on their findings, which recommend certain interventions for improving the screening rates for these cancers (Baron et al., 2008a; Sabatino et al., 2012; Community Preventive Services Task Force (CPSTF), 2013). The guidelines also aid decision makers in choosing an appropriate intervention (Townsend et al., 2009; Blumenthal et al., 2010; Lobb et al., 2011; Hannon et al., 2012).

In Japan, there are no guidelines on the types of strategies that improve cancer screening rates. Some studies have previously evaluated the effectiveness of various strategies (Hisamichi et al., 1991; Watanabe, 2003; Shimada et al., 2010a; Shimada et al., 2010b; Matsuda et al., 2011; Takaku, 2011; Kuroki, 2012; Yoshida et al., 2012), but it was difficult to compare the effectiveness of these strategies, as each study focused on

[1]*Faculty of Economics, Shiga University, Shiga,* [2]*The Hakubi Center of Advanced Research, Graduate School of Economics, Kyoto University, Kyoto,* [3]*Cancer Screening Assessment and Management Division, Research Center for Cancer Prevention and Screening, National Cancer Center, Tokyo, Japan* **For correspondence: hi-sano@biwako.shiga-u.ac.jp*

the effectiveness of an individual strategy using different subjects and methodologies. As the most effective strategy in improving cancer screening rates differs depending on the country and region (McAvoy and Raza, 1991; King et al., 1994; Saywell et al., 1999; Champion et al., 2003; Saywell et al., 2003; Saywell et al., 2004; Blumenthal at al., 2010; Lee et al., 2012; Frie et al., 2013), it remains unclear which strategy would be the most effective in Japan. Therefore, a study comparing the effectiveness of different strategies used to improve cancer screening rates in Japan is warranted and poised to be very useful for decision makers.

The aim of the present study was to quantitatively evaluate the relationships between cancer screening rates and strategies used to improve screening rates, as well as to determine which strategy is the most effective in Japan.

## Materials and Methods

*Subjects*

The subjects were selected from a total of 1,746 municipalities that conducted gastric, lung, colorectal, cervical, and breast cancer screening in Japan. Cancer screening rates of municipalities were determined from data in the Report on Regional Public Health Services and Health Promotion Services between April 2009 and March 2010, which was prepared by the Ministry of Health, Labour, and Welfare (MHLW, 2010). In this report, the number of participants and persons eligible for the cancer screenings was tallied by sex and age in 1,746 municipalities. Persons eligible for the cancer screenings conducted by municipalities included women aged ≥20 years for cervical cancer screening, women aged ≥40 years for breast cancer screening, and both men and women aged ≥40 years for other cancer screenings. Using this report, the following characteristics of municipalities were determined: the number of eligible persons, the ratio of males to females, and percentage of those aged ≥65 years.

Data on strategies implemented by each municipality for cancer screening were obtained from a survey on the implementation of cancer screening among the different municipalities, which was conducted by the MHLW in January 2010. In this survey, the MHLW collected data on the content of examinations, strategies, and out-of-pocket costs for cancer screening among the different municipalities. 1,740 of all municipalities (99.7%) had responded to this survey. The CDC recommends interventions that use client reminders and small media, and interventions that include one-on-one education by telephone or via face-to-face encounters for colorectal, cervical, and breast cancer screening (Sabatino et al., 2012). It also recommends interventions that make screening accessible and easier for colorectal and breast cancer, and reduce out-of-pocket costs for breast cancer screening (Baron et al., 2008a; Sabatino et al., 2012; CPSTF, 2013). Based on these recommendations, similar strategies were assessed, in particular: sending personal invitation letters, personal visitations by community health workers, number of individuals screened in a clinical setting, and free screening. The use of newsletters in place of small media was not evaluated because about 90% of municipalities already implemented this strategy.

**Table 1. Characteristics of Cancer Screening in Japan between April 2009 and March 2010**

| Variable | Gastric | Lung | Colorectal | Cervical | Breast |
|---|---|---|---|---|---|
| All municipalities | | | | | |
| Number of municipalities | 1,718 | 1,610 | 1,726 | 1,717 | 1,693 |
| Screening rate(%): mean (S.D.) | 15.8 (12.0) | 27.4 (18.9) | 21.4 (13.6) | 16.9 (10.4) | 13.2 (10.8) |
| Strategies | | | | | |
| Sending personal invitation letters: n (%) | 946 (55.1) | 889 (55.2) | 947 (54.9) | 966 (56.3) | 933 (55.1) |
| Personal visitations by community health workers: n (%) | 105 (6.1) | 99 (6.2) | 107 (6.2) | 104 (6.1) | 102 (6.0) |
| Number of individuals screened in clinical settings: mean (S.D.) | 613 (2,891) | 1,369 (6,582) | 1,947 (6,967) | 1,691 (5,091) | 759 (2,706) |
| Free screening: n (%) | 143 (8.3) | 362 (22.5) | 167 (9.7) | 161 (9.4) | 119 (7.0) |
| Characteristics of eligible persons | | | | | |
| Number of eligible persons: mean (S.D.) | 22,315 (47,190) | 22,821 (43,855) | 22,946 (49,320) | 18,701 (41,438) | 13,747 (29,503) |
| Ratio of males to females: mean (S.D.) | 0.73 (0.16) | 0.72 (0.17) | 0.73 (0.17) | - | - |
| Percentage of those aged ≥65 years: mean (S.D.) | 52.9 (12.1) | 53.4 (12.3) | 53.0 (12.1) | 42.6 (13.0) | 53.2 (11.9) |
| Large municipalities (population ≥30,000) | | | | | |
| Number of municipalities | 809 | 767 | 812 | 808 | 800 |
| Screening rate(%): mean (S.D.) | 12.3 (9.0) | 22.1 (15.7) | 18.3 (10.9) | 15.2 (8.1) | 12.2 (8.6) |
| Strategies | | | | | |
| Sending personal invitation letters: n (%) | 407 (50.3) | 396 (51.6) | 416 (51.2) | 422 (52.2) | 406 (50.8) |
| Personal visitations by community health workers: n (%) | 24 (3.0) | 21 (2.7) | 24 (3.0) | 22 (2.7) | 22 (2.8) |
| Number of individuals screened in clinical settings: mean (S.D.) | 1,255 (4,116) | 2,806 (9,326) | 4,052 (9,736) | 3,455 (7,011) | 1,538 (3,786) |
| Free screening: n (%) | 70 (8.7) | 162 (21.1) | 79 (9.7) | 75 (9.3) | 45 (5.6) |
| Characteristics of eligible persons | | | | | |
| Number of eligible persons: mean (S.D.) | 42,401 (62,911) | 43,018 (57,003) | 43,709 (65,937) | 36,094 (55,436) | 26,134 (39,346) |
| Ratio of males to females: mean (S.D.) | 0.69 (0.17) | 0.68 (0.17) | 0.69 (0.17) | - | - |
| Percentage of those aged ≥65 years: mean (S.D.) | 52.0 (12.4) | 52.3 (12.5) | 52.0 (12.4) | 39.8 (12.2) | 51.5 (11.4) |
| Small municipalities (population <30,000) | | | | | |
| Number of municipalities | 909 | 843 | 914 | 909 | 893 |
| Screening rate(%): mean (S.D.) | 18.9 (13.4) | 32.2 (20.2) | 24.1 (15.0) | 18.4 (11.9) | 14.2 (12.4) |
| Strategies | | | | | |
| Sending personal invitation letters: n (%) | 539 (59.3) | 493 (58.5) | 531 (58.1) | 544 (59.9) | 527 (59.0) |
| Personal visitations by community health workers: n (%) | 81 (8.9) | 78 (9.3) | 83 (9.1) | 82 (9.0) | 80 (9.0) |
| Number of individuals screened in clinical settings: mean (S.D.) | 41 (175) | 62 (263) | 78 (285) | 122 (228) | 62 (127) |
| Free screening: n (%) | 73 (8.0) | 200 (23.7) | 88 (9.6) | 86 (9.5) | 74 (8.3) |
| Characteristics of eligible persons | | | | | |
| Number of eligible persons: mean (S.D.) | 4,439 (3,126) | 4,445 (3,084) | 4,500 (3,124) | 3,241 (2,321) | 2,650 (1,864) |
| Ratio of males to females: mean (S.D.) | 0.77 (0.15) | 0.76 (0.16) | 0.77 (0.16) | - | - |
| Percentage of those aged ≥65 years: mean (S.D.) | 53.8 (11.8) | 54.5 (12.1) | 53.9 (11.8) | 45.0 (13.1) | 54.8 (12.1) |

Municipalities were excluded from the study if there were missing values in these variables or <10 eligible persons. Furthermore, municipalities were also excluded if they did not perform the following examinations: gastric X-ray for gastric cancer, chest X-ray for lung cancer, fecal occult blood tests for colorectal cancer, Pap smear for cervical cancer, and mammography for breast cancer. These examinations are recommended for population-based screening as there is sufficient evidence to suggest that these tests reduce the cancer mortality rate in Japan (Hamashima et al., 2008; Hamashima et al., 2010; National cancer center, 2013). Of all municipalities, 1,718 (98.4%), 1,610 (92.2%), 1,726 (98.9%), 1,717 (98.3%), and 1,693 (97.0%) municipalities were included in the analyses for gastric, lung, colorectal, cervical, and breast cancer screening, respectively.

*Statistical analysis*

Partial correlation coefficients were calculated to quantitatively evaluate the relationships between cancer screening rates and the strategies used to improve screening rates in various municipalities. The coefficients indicate how closely each strategy is related to the cancer screening rate after excluding the effects of confounding factors, including the other three strategies, the number of eligible persons, the ratio of males to females, and the percentage of elderly.

The relationships between cancer screening rates and the strategies may vary with the population size of the municipalities. Therefore, partial correlation coefficients were also separately calculated for large municipalities (with populations of over 30,000) and small municipalities (with populations of under 30,000). In 2009, a municipality was seen as a city if the population was over 30,000, but seen as a town or village if not. All analyses were performed using STATA version 12 (StataCorp, College Station, TX, USA).

## Results

The characteristics of cancer screening in Japan are presented in Table 1. The average screening rates for gastric, lung, colorectal, cervical, and breast cancer were 15.8%, 27.4%, 21.4%, 16.9%, and 13.2%, respectively. The strategy of sending invitation letters was implemented at about 55% of the municipalities, whereas personal visitations by community health workers were implemented at only 6% of all municipalities. Free screening was implemented at 23% of all municipalities for lung cancer screening and at 7-10% of all municipalities

**Table 2. Partial Correlations between Cancer Screening Rates and Strategies Used to Improve Screening Rates in Japan**

| Variable | Gastric | Lung | Colorectal | Cervical | Breast |
|---|---|---|---|---|---|
| | All municipalities | | | | |
| Number of municipalities | 1,718 | 1,610 | 1,726 | 1,717 | 1,693 |
| Strategies | | | | | |
| Sending personal invitation letters d | 0.28[a] | 0.32[a] | 0.30[a] | 0.26[a] | 0.13[a] |
| Personal visitations by community health workers d | 0.23[a] | 0.15[a] | 0.22[a] | 0.18[a] | 0.12[a] |
| Number of individuals screened in clinical settings | 0.17[a] | 0.19[a] | 0.21[a] | 0.25[a] | 0.18[a] |
| Free screening d | 0.03 | 0.13[a] | 0.06[b] | 0.08[a] | 0.01 |
| Characteristics of eligible persons | | | | | |
| Number of eligible persons | -0.24[a] | -0.26[a] | -0.23[a] | -0.28[a] | -0.21[a] |
| Ratio of males to females | 0.07[a] | 0.09[a] | 0.03 | - | - |
| Percentage of those aged ≥65 years | 0.07[a] | 0.20[a] | 0.12[a] | -0.01 | -0.13[a] |
| | Large municipalities (population ≥30,000) | | | | |
| Number of municipalities | 809 | 767 | 812 | 808 | 800 |
| Strategies | | | | | |
| Sending personal invitation letters d | 0.39[a] | 0.39[a] | 0.36[a] | 0.30[a] | 0.17[a] |
| Personal visitations by community health workers d | 0.15[a] | 0.11[a] | 0.15[a] | 0.06[c] | 0.07[b] |
| Number of individuals screened in clinical settings | 0.28[a] | 0.31[a] | 0.35[a] | 0.41[a] | 0.28[a] |
| Free screening d | 0.05 | 0.14[a] | 0.08[b] | 0.04 | 0.03 |
| Characteristics of eligible persons | | | | | |
| Number of eligible persons | -0.32[a] | -0.32[a] | -0.33[a] | -0.43[a] | -0.31[a] |
| Ratio of males to females | -0.02 | 0.02 | -0.07[b] | - | - |
| Percentage of those aged ≥65 years | 0.05 | 0.17[a] | 0.03 | 0.01 | -0.06[c] |
| | Small municipalities (population <30,000) | | | | |
| Number of municipalities | 909 | 843 | 914 | 909 | 893 |
| Strategies | | | | | |
| Sending personal invitation letters d | 0.25[a] | 0.30[a] | 0.29[a] | 0.24[a] | 0.11[a] |
| Personal visitations by community health workers d | 0.22[a] | 0.13[a] | 0.22[a] | 0.20[a] | 0.12[a] |
| Number of individuals screened in clinical settings | 0.15[a] | 0.09[a] | 0.11[a] | 0.20[a] | 0.19[a] |
| Free screening d | 0.02 | 0.13[a] | 0.02 | 0.09[a] | 0.00 |
| Characteristics of eligible persons | | | | | |
| Number of eligible persons | -0.36[a] | -0.29[a] | -0.34[a] | -0.36[a] | -0.28[a] |
| Ratio of males to females | -0.01 | 0.02 | -0.02 | - | - |
| Percentage of those aged ≥65 years | 0.01 | 0.16[a] | 0.10[a] | -0.05 | -0.15[a] |

*[a]p values ≤0.01; [b]p values ≤0.05; [c]p values ≤0.1; [d]Dummy variables

for other types of cancer screening. The average number of individuals that had been screened in the clinical setting was the largest for colorectal cancer screening, and the smallest for gastric cancer screening.

The average cancer screening rates were higher in small municipalities than large municipalities for all cancer screening. Personal visitations by health workers were implemented in about 9% of all small municipalities, which was about 6% higher than that of large municipalities for all screenings. The average number of individuals screened in the clinical setting of large municipalities was more than 20-fold greater than that of small municipalities for all cancer screening. This may be because many small municipalities did not implement cancer screening in the clinical setting (i.e., about 80% for gastric, lung, and colorectal cancers, 27% for cervical cancers, and 43% for breast cancers).

The partial correlation coefficients for the relationships between cancer screening rates and the strategies used in Japan are presented in Table 2. In all municipalities, there were positive correlations between the screening rates for all cancers and the strategies used, with the exception of free screening ($p<0.01$). Of the four strategies, sending personal invitation letters had the highest correlation coefficients with cancer screening rates. They were as follows: 0.28 for gastric cancer screening, 0.32 for lung cancer screening, 0.30 for colorectal cancer screening, and 0.26 for cervical cancer screening. For cervical cancer screening, the correlation between the number of individuals screened in the clinical setting and the screening rates was similar to that of sending invitation letters. For breast cancer screening, all strategies had a low or no correlation with the screening rates in all municipalities.

In large municipalities, the correlation coefficients between sending invitation letters and the screening rates were relatively high. Specifically, they were as follows: 0.39 for gastric cancer screening, 0.39 for lung cancer screening, 0.36 for colorectal cancer screening, and 0.30 for cervical cancer screening. In large municipalities, the correlation coefficients between the number of individuals screened in the clinical setting and the screening rates were also relatively high, particularly for cervical cancer screening ($r=0.41$). For breast cancer screening, the correlation coefficient rose to 0.28 in large municipalities. In small municipalities, the correlation coefficients between cancer screening rates and the strategies used were similar to those of all municipalities, with the exception of the number of individuals screened in the clinical setting.

## Discussion

In Japan, the National Cancer Control Plan was published in 2007 with the aim of increasing cancer screening rates above 50% within 5 years (MHLW, 2012a). To achieve this goal, municipalities had to implement effective strategies that would increase screening for various types of cancer. Previous studies have shown that sending personal invitation letters (Watanabe, 2003; Shimada et al., 2010a; Shimada et al., 2010b; Matsuda et al., 2011), distributing leaflets and pamphlets (Hisamichi et al., 1991; Yoshida et al., 2012), and increasing the availability of cancer screening in clinical settings (Takaku, 2011) were effective in improving cancer screening rates in Japan. However, it was unclear which strategy was the most effective. In the present study, after excluding the effects of confounding factors, correlations between four different strategies and cancer screening rates were evaluated.

Of all strategies, sending personal invitation letters had the highest positive correlations with screening rates for gastric, lung, colorectal, and cervical cancers. This strategy appears to be particularly effective in improving cancer screening rates in large municipalities. In most Western countries, the importance of a national call-recall system, which gives call and recall notifications by mail or telephone, is well recognized by the government for the purposes of increasing cancer screening (Quinn et al., 1998; Baron et al., 2008b). In Japan, municipalities are responsible for implementing strategies to improve cancer screening rates. However, nearly half of the municipalities did not implement this strategy. To improve cancer screening rates, all municipalities need to prioritize establishing a system that sends personal invitation letters for cancer screening.

The number of individuals that had been screened in the clinical setting also demonstrated positive correlations with all cancer screening in large municipalities. The correlation was particularly high for cervical cancer screening. Previous studies reported on the effectiveness of making access to screening easier by reducing the time or distance between the service delivery settings and the examinees in increasing colorectal and breast cancer screening in Western countries (Dolan et al., 1999; Baron et al., 2008c). Thus, increasing the availability of screening in the clinical setting should be effective in improving the screening rates for not only colorectal and breast cancer, but also for cervical cancer, in Japan. However, the quality assurance of cancer screening in the clinical settings was insufficient compared to that of mass screening in Japan (Arisue et al., 2007; Osaka City, 2010). Additionally, many small municipalities did not implement cancer screening in the clinical setting (i.e., about 80% for gastric, lung, and colorectal cancers, 27% for cervical cancers, and 43% for breast cancers). This may be due to several reasons. For example, small municipalities have been under more severe fiscal constraints than large municipalities (Ministry of Internal Affairs and Communications, 2011), and consequently are more likely not to have any incentives for increasing cancer screening in the clinical settings (Takaku, 2011). Thus, to increase cancer screening in the clinical setting, particularly in small municipalities, these problems need to be resolved.

Personal visitations by community health workers had low, but positive, correlations with cancer screening rates compared to sending invitation letters and the number of individuals that were screened in the clinical setting. However, these correlations were higher in small municipalities versus large municipalities. This may be because this strategy was implemented better in small municipalities than large municipalities. This strategy is unlikely to be implemented in large municipalities because it is difficult to employ many community health workers for the number of eligible persons. It was previously reported that the cost effectiveness of one-on-one education per additional mammogram increased substantially if the cost of labor increased (Stockdale et al., 2000). Thus, each municipality needs to pay sufficient attention to fiscal constraints and decide whether to implement this strategy.

Free screening had a weak correlation with cancer screening rates. To improve screening rates, the MHLW had initiated a strategy that distributed free coupons to some individuals for breast and cervical cancer screening beginning in 2009 and for colorectal cancer screening beginning in 2011. The distribution of free coupons improved the screening rates for women who had not been screened for cervical cancer in Fukuoka Prefecture (Kuroki, 2012). However, changes in price for cancer screenings had little influence on demand for screenings in Hokkaido Prefecture (Takemura et al., 2001). The CDC recommends interventions that reduce out-of-pocket costs for breast cancer screening, but does not recommend such interventions for cervical and colorectal cancer screening due to insufficient evidence (Baron et al., 2008a; Sabatino et al., 2012; CPSTF, 2013). Therefore, reducing the out-of-pocket costs alone appears to be insufficient for improving the cancer screening rates.

However, it should be mentioned that none of the strategies had strong (or very high) correlations with cancer screening rates. For breast cancer screening, even sending personal invitations had a very low correlation with the screening rates. Therefore, just sending personal invitation letters and increasing the availability of screening in the clinical settings does not appear to greatly improve the cancer screening rates. The CDC recommends provider-oriented interventions, which evaluate the providers' performance and present the providers with the results, to increase cancer screening (Sabatino et al, 2008). The MHLW reported that implementing cancer screening and specific health checkups simultaneously improved cancer screening rates in some municipalities (MHLW, 2012b). In addition to these strategies, future studies that determine other effective strategies for improving cancer screening rates are warranted, including where screening occurs and the medical personnel involved (Tsunematsu et al., 2013).

This study has several limitations that need to be discussed. First, while using partial correlation analysis to determine the relationships between cancer screening rates and the strategies has provided some foundational knowledge on the topic, the causality of these relationships is still unclear. It is also necessary to consider that these findings may be a result of reverse causality, meaning that the implementation of strategies is influenced by cancer screening rates. Second, data on costs of the strategies implemented by each municipality could not be used in the analyses (Saywell et al., 1999; Stockdale et al., 2000; Saywell et al., 2003; Saywell et al., 2004). The cost-effectiveness of these strategies should be evaluated. Third, some municipalities might have conducted cancer screening not for all eligible persons but for very limited persons, such as those who sought to receive screening or had received a year before. Such municipalities should be excluded in the analyses. Fourth, it is necessary to further evaluate which strategies are more effective than those studied herein.

In conclusion, of the strategies used to improve cancer screening rates, sending personal invitation letters had the greatest positive correlations with screening rates for gastric, lung, colorectal, and cervical cancers. This strategy appears to be particularly effective in improving cancer screening rates in large municipalities. All municipalities should predominantly focus on establishing a system that sends personal invitation letters for cancer screening. In large municipalities, increasing the availability of screening in the clinical setting may also be effective in improving cancer screening rates.

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# V. 参 考 資 料

別添①

# 子宮頸がん検診における HPV 検査の有効性評価研究

# 研究実施計画書

― 平成 26 年 4 月 8 日　第 1 版 ―
― 平成 27 年 2 月 3 日　第 2 版 ―

# 目次

## 0. 概要

### 0.1. 目的

子宮頸がん検診は従来、死亡率減少効果が科学的に証明されている細胞診で実施されてきた。しかし、近年前がん病変やがんの早期発見が可能であるとして、子宮頸がん検診へのヒトパピローマウイルス（HPV）検査の導入が検討されている。平成25年度には厚生労働省によるがん検診推進事業において、一定の精度管理が行われている自治体の30、35、40歳を対象にHPV検査を実施するHPV検査検証事業が実施され、この事業の効果を評価するため、対象自治体における検診受診者コホート研究を立ち上げ、実施している（慶應義塾大学医学部倫理審査承認済：承認番号20130139）。このコホート研究は自治体の検診事業の途中から研究登録を開始したため、十分なサンプルサイズが得られなかった上に、平成26年度は厚生労働省によるHPV検査検証事業が実施されなかった。よって、子宮頸がん検診におけるHPV検査の有効性を検討するために、研究の意義に賛同し、協力の得られる自治体を対象に、細胞診とHPV検査を併用で実施する介入研究を実施することとした。この研究と平成25年度に開始した子宮頸がん検診受診者コホート研究を合せて、検診の方法別の子宮頸部上皮内腫瘍（Cervical Intraepithelial Neoplasia2, 3 （CIN2、CIN3））、浸潤がんの感度、特異度や発見に関する指標、治療内容や死亡率を観測することができる。

### 0.2. 適格規準

研究対象自治体において自治体が実施する子宮頸がん検診を受診した30-49歳の女性とする。このうち、以下の①～④に該当する場合は研究対象外とする。

① 過去に子宮頸がん（浸潤がん）にかかったことがある方
② 過去に子宮頸部の手術（円錐切除術）を受けたことがある方
③ 過去に子宮摘出の手術を受けたことがある方
④ 現在、子宮頸部の異常（異形成や細胞診異常）の経過観察中の方

### 0.3. 目標登録者数

細胞診検査とHPV検査併用群（介入群）と細胞診検査のみの群（対照群）においてそれぞれ2万から2万5千人を予定している。

すでに平成25年に開始している「子宮頸がん検診受診者コホート研究」（慶應義塾大学医学部倫理審査承認済：承認番号20130139）と合わせた目標登録症例数である。

### 0.4. 研究期間

（登録期間）研究許可日～2016年3月末
（追跡期間）登録から7年間：研究登録日～2023年3月末
（解析期間）追跡終了から5年以内：2023年3月末～2028年3月末