Author's response to reviews

Title: Effect of providing risk information on undergoing cervical cancer screening: a randomized controlled trial

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Author's response to reviews: see over
Responses to reviewers’ comments

Reviewer 1

**Major comment**

1) This study compares no invitation with an invitation including benefit information and an invitation including benefit and harm information. It is already well established that postal invitations increase uptake of cervical screening, so the comparing of the control group with the intervention groups adds little to the existing literature.

→Thank you very much for carefully reviewing our paper. It is true that there already exists established evidence that postal invitations increase uptake of cervical cancer screening. Sabatino and colleagues reviewed interventions with the aim of improving the cervical cancer screening rate and found strong evidence of effectiveness (American Journal of Preventive Medicine, 2012). However, the extant evidence is mainly based on interventions for the general population in Europe and the United States, and the effectiveness of interventions among non-adherent or Asian populations has been scarcely evaluated until now. As our study investigated the Japanese non-adherent population in cervical cancer screening as participants, we believe that the results of our survey about the effectiveness of postal reminders on screening attendance broaden the knowledge of previous studies.

2) The comparison of the two information formats is interesting, but both are extremely brief, and information about possible harm arising from (sometimes unnecessary) treatment was not included, I think could limit the validity of the study.

→We thank the reviewer for this helpful comment. Please see the revised version of Table 1 for the information included in each reminder. In fact, information about the possible risks of screening includes the possibility of false negatives and interval cancer, the possibility of false negatives and unnecessary treatment, and the possibility of overdiagnosis. The descriptions of the messages were revised as follows: Possibility of false negatives and interval cancer—“The accuracy of screening is not 100%. There is a risk of interval cancer.” Possibility of false positives and unnecessary treatment—“More than 90% of positive or suspicious patients will not be diagnosed with cervical cancer. There is a risk of receiving unnecessary treatment.” Possibility of overdiagnosis—“It cannot determine whether detected cancer should be treated or not. You should talk with your doctor about how to treat the disease.”
It is true that there has been a movement towards informed choice in the public health domain. However, screening invitations usually do not include information about major potential harms of screening. Jørgensen and Gøtzsche published a survey on the quality of information used in mammography screening programs (BMJ, 2006). The paper found that major harms of screening were not mentioned in any of 31 invitations.

In addition, Gigerenzer and colleagues recently reported a European survey of the continuing dramatic overestimation of the possible benefits of mammography and prostate-specific antigen testing in the vast majority of women and men (National Cancer Institute, 2009). In the article, the authors found that frequent consulting of physicians and health pamphlets tended to increase rather than reduce overestimation.

Therefore, we believe that estimating the effects of intervention with information on possible benefits and harms of screening on screening attendance and informed choice will add important new knowledge with significant practical implications for the field. To illustrate this point, changes in the manuscript (third paragraph of the introduction) were made as follows: “In fact, screening invitations generally do not include information about the major harms of screening. Jørgensen and Gøtzsche published a survey on the quality of information used in mammography screening programs [12], finding that the major harms of screening were not mentioned in any of the 31 invitations. In addition, Gigerenzer and colleagues recently reported a European survey on the continuing dramatic overestimation of the possible benefits of mammography and prostate-specific antigen testing in the vast majority of women and men [13]. In the article, the
authors found that frequent consulting of physicians and health pamphlets tended to increase rather than reduce overestimation.”

Minor revisions

Abstract

4) Please make clear in the abstract that the participants are non-adherent to screening.

→Thank you very much for pointing this out. Changes in the manuscript (Methods, Lines 1–2) were made as follows: “In total, 1,912 women aged 20–39 years who had not participated in screening in the fiscal year were selected from a Japanese urban community setting.”

Introduction

5) It would be useful to know what the incidence of cervical cancer is in Japan.

→Thank you very much for this helpful comment. Changes in the introduction (first paragraph) were made as follows: “Cervical cancer is one of the most common cancers among women [1]. It is estimated that 275,100 women died of cervical cancer in 2008 [1]. Further, the incidence of cervical cancer in Japan was 9,794 in 2008 [2].”

Methods

6) Please clarify the usual screening programme. Do women ever receive a postal invitation, or is the information about screening simply available online and via a newsletter? Does the newsletter get delivered to people’s homes?

→Thank you very much for pointing this out. Changes in the manuscript (first paragraph of Setting) were made as follows: “The local municipality’s website and monthly community newsletter that is mailed to residents offer information about the screening program. No other invitations were available previously.”

7) How was non-adherence to screening defined? The authors state that screening is annual to triennial. Were women included if they had not been screened within the last 3 years?

→Thank you for asking this important question. Changes in the manuscript (first paragraph of Procedure) were made as follows: “We selected women aged 20–39
years who had not participated in the screening in 2013 as non-adherent participants for this study."

8) It seems that one of the major harms of screening (unnecessary treatment and possible adverse consequences of this) is missing from the information. Did the authors consider including this information?

→ Please see the comment in response to 2).

9) The authors refer to ‘demographic characteristics’ of the sample but only age is shown in Table 2. Did they have any other information, such as social class or ethnic background?

→ Please see the revised version of Table 2 for age and cervical cancer screening experience of participants. Unfortunately, we could not identify other demographic characteristics because of data limitations in the local municipality. Only age and sex data were available.

Table 2 Age and screening experience among the groups

<table>
<thead>
<tr>
<th>Age groups (years)</th>
<th>Group A (n = 622)</th>
<th>Group B (n = 640)</th>
<th>Group C (n = 650)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intervention group (benefit)</td>
<td>Intervention group (benefit + nsk)</td>
<td>Control group (simple)</td>
<td></td>
</tr>
<tr>
<td>Mean (SD) age (years)</td>
<td>29.6 (4.5)</td>
<td>31.4 (4.2)</td>
<td>31.0 (4.3)</td>
<td>0.413a</td>
</tr>
<tr>
<td>Age groups (years):</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20–29</td>
<td>270 (42.3)</td>
<td>295 (46.1)</td>
<td>275 (43.4)</td>
<td>0.372b</td>
</tr>
<tr>
<td>30–39</td>
<td>352 (57.7)</td>
<td>345 (53.9)</td>
<td>375 (56.6)</td>
<td></td>
</tr>
<tr>
<td>Screening during 2 years before study</td>
<td>11 (1.7)</td>
<td>14 (2.2)</td>
<td>23 (3.4)</td>
<td>0.112c</td>
</tr>
</tbody>
</table>

Values are presented as n (%)

a. p-value for comparison of age distribution between three groups by one-way ANOVA.
b. p-value for comparison of age proportion between three groups by chi-squared test.
c. p-value for comparison of cervical cancer screening experience between three groups by one-way ANOVA.

Results

10) I found Figure 2 quite hard to look at – perhaps a more conventional table showing the level of uptake odds ratios for attendance in each group would be a clearer format?

Thank you for this suggestion. Changes were made as follows (Tables 3 and 4):

Table 3 Effect of the intervention on cervical cancer screening rate
Table 4 Differences in the effect of the intervention by message type

<table>
<thead>
<tr>
<th>Group</th>
<th>Attendance n (%)</th>
<th>OR</th>
<th>95%CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A</td>
<td>Intervention group (benefit)</td>
<td>71 (11.4)</td>
<td>2.49</td>
<td>1.61–3.84</td>
</tr>
<tr>
<td>Group B</td>
<td>Intervention group (benefit + risk)</td>
<td>66 (10.3)</td>
<td>2.22</td>
<td>1.43–3.84</td>
</tr>
<tr>
<td>Group C</td>
<td>Control group (simple)</td>
<td>32 (4.9)</td>
<td>1 (reference)</td>
<td>–</td>
</tr>
</tbody>
</table>

Values are presented as n (%)

OR: odds ratio, CI: confidential interval, p-value for comparison of cervical cancer screening rate between groups by logistic regression analysis.

11) There were minor language errors throughout the manuscript which could be corrected by a native speaker.

→ Thank you for pointing this out. The manuscript has been reviewed by a native speaker and is now free of such language errors.
Reviewer 2

**Major points**

1) Explanations for the results are insufficient, even considering the some limitations of this study the authors described. At least, the demographics of the participants including age distribution and the history of Pap test should be shown.

→ Thank you very much for carefully reviewing our paper. Please see the revised version of Table 2 for age and screening experience among the groups. Unfortunately, we could not identify other demographic characteristics because of data limitations in the local municipality. Only age and sex data were available.

Table 2 Age and screening experience among the groups

<table>
<thead>
<tr>
<th></th>
<th>Group A (n = 622): Intervention group (benefit)</th>
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</table>

Values are presented as n (%)

a. p-value for comparison of age distribution between three groups by one-way ANOVA.
b. p-value for comparison of age proportion between three groups by chi-squared test.
c. p-value for comparison of cervical cancer screening experience between three groups by one-way ANOVA.

2) As a control group, the women allocated in Group C received nothing. The possibility that the documents sent to the target women in Group A and B played a role as a simple reminder of cervical cancer screening, indifferent to the information, should be discussed.

→ We apologize for the mistake in our wording here. Group C actually received a simple reminder during the intervention period from the local government. As such, this study compared the effect of “reminder + additional information” with “simple reminder.”

**Minor points**

3) In the abstract, using the word “patients” is inappropriate to describe the target women of cervical cancer screening.

→ Thank you very much for pointing this out. Changes in the manuscript (Abstract: Background) were made as follows: “In Japan, the cervical cancer screening rate is extremely low. Towards improving the cervical cancer
screening rate, encouraging eligible people to make an informed choice, which is a decision-making process that relies on beliefs informed by adequate information about the possible benefits and risks of screening, has attracted increased attention in the public health domain.”

4) Concerning the cervical cancer screening rate (32.4%) in the introduction, the source of the data and the calculation method should be clarified.

→Thank you very much for this suggestion. Changes in the manuscript (first paragraph of introduction) were made as follows: “Given that the cervical cancer screening rate in Japan is extremely low (32.7%, attendance rate in a year) [5], increasing the screening rate is one of the most important public health issues.”


5) The authors stated that the screening program was an annual to triennial Pap smear and HPV DNA testing for women over 20 years. Does it mean that every target woman has HPV DNA testing even for the annual screening?

→Thank you very much for noting this area in need of clarification. Changes in the manuscript (first paragraph of Setting) were made as follows: “In the area, the provided screening program was an annual to triennial Pap smear and human papillomavirus (HPV) DNA testing for women over 20 years old. The interval between screening varies by test results. Participants with positive Pap smear results are offered extensive screening. If the results of the Pap smear are negative, participants with positive results of the HPV DNA testing are offered to take screening again in the next year. If both of the results are negative, the participants are offered to take screening after 3 years.”

6) The style to show the reference #10 in the discussion is inadequate.

→Thank you very much for pointing this out. Changes in the manuscript (second paragraph of the discussion) were made as follows: “Although previous studies have suggested that providing information about both risks and benefits of screening enhances informed choice, the effects on screening rate have been inconclusive [14]. Moreover, these studies have evaluated the effectiveness of interventions for breast, colorectal, and prostate cancer screening, and studies for cervical cancer screening have been limited.”
Once again, we are deeply indebted to the reviewers for their insightful comments and critiques, which have enabled us to strengthen our presentation of this important study.

We thank the editor for giving us the opportunity to revise our manuscript in accordance with the reviewers’ comments.

Kindest regards,
Hiroyuki Fujiwara, MD