A quasi-randomized trial on the effectiveness of an invitation letter to improve participation in a setting of opportunistic screening for cervical cancer

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The objective of the study was to assess the effect of an invitation letter on the level of participation in a setting of mainly opportunistic screening for cervical cancer and to do a cost analysis of this intervention. We designed a quasi-randomized trial in which a sample of women between the ages of 25 and 64 years and residing in the province of Limburg, Belgium, who had no Pap smear taken in the past 30 months according to LIKAR (Limburg Cancer Registry), were assigned to an intervention group or to a control group. A written invitation was sent to 43,523 women in the intervention group. Baseline participation in cervical screening was recorded in the year before the intervention to determine its effect. Differences in cumulative incidence between the intervention and the control group were used to report the effect. The net effect of a written invitation resulted in 3,355 more women undergoing a Pap smear, which is an increase of 6.4% (95% confidence interval: 5.9–6.9). The cost per additional Pap smear taken amounted to €29.8. Within an opportunistic cervical cancer screening setting, the effect of a registry-based invitational programme to nonattenders increases the participation further, and at no extra cost compared with an invitational programme to all screen-eligible women irrespective of their screening status. European Journal of Cancer Prevention 17:238–242 © 2008 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Introduction

Organized cervical screening programmes have been shown to reduce cancer-related mortality. As a result, local health authorities were requested by the government of the Flemish community in 1994 to organize and implement a cervical screening programme according to the 1992 guidelines of the European Commission ‘Europe against Cancer’ (Coleman et al., 1993). The aim of this European campaign was to fight cervical cancer by screening women ideally in the age category of 25–64 years (Lynge, 2000). Since then, every 3 years most women in Flanders (the northern part of Belgium) receive an invitation by mail to undergo a Pap smear. These invitations are administered by the local health authorities and are based on identification through the population registry. In Flanders, screening for cervical cancer remains mainly opportunistic in nature, characterized by a high level of participation through self-referral inherent to a social health system with a low-threshold access to health care providers. Screening coverage for the region is high and estimated to be between 70 and 80% over a period of 5 years (Arbyn et al., 1997; Desmaret et al., 1997).

Although letter reminders have shown a consistent increase in participation rate irrespective of differences in health care systems (Forbes et al., 1999; Tseng et al., 2001), it is not clear whether an invitational programme in a population with a high intrinsic participation through opportunistic cervical screening is cost-effective. Therefore, LIKAR (Limburg Cancer Registry), governing the database of the cervical screening status of all women in the province of Limburg since 1996, opted to change the existing screening strategy based on a 3-yearly invitation to all screen-eligible women irrespective of screening status to a selective invitational programme to nonattenders. The aim of the study was to determine the benefit and cost of such a registry-based invitation to nonattenders in a well-defined population with known high participation in cervical screening.

Patients and methods

In the province of Limburg, with 215,000 women eligible for cervical testing, a programme of written invitations to nonattenders was started in November 2001. Women between 25 and 64 years of age were identified through the population registry and those who had no Pap smear done in the past 30 months, according to the LIKAR registry on cervical cytology, were eligible for the study. The 30-month period was chosen as it was just short of the 3-year invitation cycle in use at that time. Data on cervical cytology, irrespective of whether test results were
obtained through organized or opportunistic screening, were collected quarterly from the pathology laboratories in an encrypted format according to a unidirectional hashing algorithm. Data were administered by LIKAR. To run an accurate database in a densely populated region such as Flanders, LIKAR was compelled to establish a network with pathology laboratories in the neighbouring provinces. This was the only way to trace cytology reports of women domiciled in the province of Limburg but having had their Pap smears reported and registered in pathology laboratories outside the province. This was indeed a realistic scenario for women living on the boundaries of the province. The cytology registry was computer-linked to the population registry by the Expertise Centre for Digital Media at the University of Limburg. To do so, a list of anonymized codes of screened and unscreened women was generated, which was then forwarded to the medical officer in charge of the programme. After decoding the list of unscreened women, invitation letters were sent to nonattendees to have a Pap smear done by their physician of choice. It was a standard invitation letter that stated the reason for its writing and a brief description of the test and its purpose. A quasi-randomization design was chosen for practical and financial constraints: letters were posted for eight age-specific units within a 5-year age group (e.g. women born in 1976 and 1981 as a unit within the age group 25–29 years and 30–34 years, respectively). We arranged for a preintervention (baseline) recording of Pap smear uptake over a 12-month period to correct for potential differences in participation at baseline between the control and the intervention group. To master the administrative workload involved, we defined two cohorts. The first cohort, including the younger women aged 25–41 years (women born in the calendar years 1976, 1971, 1966, and 1961) and referred to as intervention group A, received their invitation letter between November 2001 and January 2002. To measure the absolute effect of an invitation letter on participation level, we took into account the number of women undergoing at least one Pap smear in a 12-month period ending on the day a letter was posted (baseline period) and the number of women undergoing a Pap smear in the next 12 months (intervention period). The baseline period is also a measure of the current level of opportunistic screening in the population. The second cohort, including older women aged 46–61 years (women born in the calendar years 1956, 1951, 1946, and 1941) and referred to as intervention group B, was invited between April and June 2002. By defining a cohort of young and older women, we also intended to test the hypothesis that an invitation letter had a larger effect on older women because of a more responsible personal health attitude. For each intervention group a control cohort of women born in the next following year was selected and followed for 12 months without receiving an invitation letter (Table 1). All women studied, both in the baseline and the intervention period, had an equal 12-month follow-up before reaching the end-of-the-study observation period.

Data were analysed according to an intention-to-treat analysis also including those women who could no longer be reached because of an untraceable change in postal address. Women who received a letter were unaware of taking part in a scientific study. This approach was a prerequisite to avoid a positive outcome bias owing to the participants knowing themselves to be studied (Hawthorne effect). The results were expressed as absolute and relative differences with 95% confidence intervals. The absolute effect of an invitation was defined as the difference in participation between the intervention and the control group and was calculated from the number of women having undergone a Pap smear in the intervention period minus the number of women having undergone a Pap smear in the baseline period (Table 2).
The relative effect was defined as the absolute effect relative to the number of women in the control group having had a Pap smear in the baseline period. The measured effect in cohorts A and B (total of eight age groups) is an indication of the effect to be anticipated in the entire screen-eligible group of women between ages 25 and 65 years (total of 40 age groups). As our study group includes a 20% random sample of the total elective population, the overall effect can simply be calculated by multiplying the number of extra women screened in the intervention group by a factor of 5.

We also performed a cost analysis of this invitational programme. Administrative co-workers were asked to note the number of working hours spent at their respective tasks in this specific effort: preparation of the list of nonattenders, hashing of data to identity number, preparation of mail, input of new data. Mailing cost was calculated at €0.5 per letter. A single invitation round, defined as the period of time it would take to invite all the nonattenders for a Pap smear, was set at 3 years.

This study was approved by the Ethics Committee of the Belgian National Cancer Registry.

**Results**

The population registry identified a total of 87,654 screen-eligible women in the 16 age-specific units that were studied. Of these women, a total of 43,523 were randomized to the intervention group and 44,131 women intended as control (Table 1). The LIKAR registry identified 151,215 women who had had no Pap smear in the past 30 months for the complete group of screen-eligible women between 25 and 64 years of age. A total of 34,569 letters were sent to women of the age-specific cohorts A(i) and B(i) eligible for screening but who had no Pap smear recorded in the LIKAR registry for the past 30 months.

The absolute net effect of invitation for the age units studied resulted in a gain of 671 women undergoing a Pap smear. The absolute net gain in the older group was significantly higher than in the younger age group (OR 1.19; 95% CI: 1.14–1.24; P < 0.001) (Table 3). For the complete screen-eligible group between the ages of 25 and 64 years this absolute net gain could be extrapolated to 3355 women (absolute net gain of 671 women per eight age units extrapolated to 40 age units).

To accomplish this return on additional Pap smears taken, a total of 1851 working hours had to be realized at an expense of €62,592 personnel costs (1 FTE = €59,515). Of these 1851 working hours, 435 h were study-specific (study activation, monitoring, data collection and analysis), 560 h were a once-off investment in the development of the programme, and 856 h of which 40 h were needed to complete the mailing and to keep the registry-based system running. Mailing costs amounted to a total of €75,607 for the 151,215 women who had had no Pap smear in the past 30 months. The cost per extra woman screened once the system is operational – thus excluding study-specific and developing cost – therefore is €29.8 (total cost of €100,100 for 3355 women that were additionally screened).

**Discussion**

Noncompliance with cervical cancer screening is an important reason why women still contract this preventable disease. Reasons for noncompliance have been identified but interventions other than patient education and reminders to reach nonattenders lag behind. This quasi-randomized study examined the effect of a new invitation to women in a well-defined population who do not participate in a programme of a 3-yearly call to have a Pap smear done. This intervention increased the proportion of women undergoing cervical testing by 6.4% (Table 3). This effect far exceeds the 1.3% (95% confidence interval −0.3–2.9%) (Eaker et al., 2004) and 2% (Morrell et al., 2005) increase in Pap smear uptake seen in two other population-based randomized

| Table 2 Cumulative incidences used to calculate the effect of recall in this study |
|----------------------------------|-----------------|-----------------|----------------------------------|
|                                  | Number of women with Pap smear | Baseline period | Postintervention | Difference |
| Intervention group               | a                | b               | b–a                |
| Control group                    | c                | d               | d–c                |
| Absolute effect of recall        | (b – a) – (d – c) |
| Relative effect of recall        | (b–a)–(d–c)/c    |

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<th>Table 3 Absolute and relative effects of an invitation on the number of women undergoing cervical testing in the next 12 months</th>
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<td>Number of women taking up Pap smear</td>
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<td>Baseline period</td>
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<td>Group A(i)</td>
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controlled trials. The Swedish study by Eaker et al. also demonstrated an increase in the number of cytological abnormalities detected by a new invitation, an effect that was even more pronounced when women received a letter reminder after 5 months.

Our study demonstrates the importance of taking into account data from a baseline observation period, which in fact amplifies the observational basis within the control group and thus more accurately defines the background effect of opportunistic participation in cervical testing. Premeasurement and postmeasurement were also necessary because a proper randomization, in which all age categories would have been represented, would equally have been excessively costly.

Strengths of this study include a well-defined population-based study group, an accurate population and LIKAR registry to direct the invitation (less than 3% of letters were returned to sender), and a randomized study design including a baseline observation period allowing an estimation of the relative net effect of recall. An important weakness of the study is that no cytological data were collected to evaluate the burden of pathology between the randomized groups. This impedes a true cost-benefit analysis. A cost-benefit estimate can be made by assuming that the pathology profile in the group of women screened additionally by the intervention is comparable to the general population. The LIKAR registry so far recorded an abnormal cytology rate of 4.85%, which would translate into an additional 163 abnormal smears discovered. Of these, about 19 would reveal a high-grade squamous intraepithelial lesion or worse (LIKAR registry 1996–2000, unpublished data). The cost of discovering one potentially preventable cancer would therefore be estimated at €268.42. This is most likely an overestimation taking into account that in the Swedish study a reminder letter increased the number of precursor lesions detected by 30% (Eaker et al., 2004). On the other hand, sending out letters to all screen-eligible women (215 000 women in the province of Limburg) every 3 years would amount to a cost of €109 131 (mailing cost €107 500 and personnel cost at €1631 calculated at 57 working hours to complete the mailing). This is a cost difference of 8.3% per 3-year cycle compared with the registry-based invitation.

A further weakness of the study was that probably too many letters of invitation were sent because of a systematic delay in data collection from the cytopathology labs (only every 3 months). This will not influence the outcome of the study results in terms of attendance rate but will have a minor negative effect on the cost analysis.

A key issue influencing the uptake of screening programmes is the accuracy of registries. Some studies of invitations for cervical screening, for example, have found that between 30 and 60% of invitations were sent to the wrong address (Austoker, 1994), which of course underestimates the effect of any recall method owing to inclusion bias.

Our study also revealed a larger effect of a letter of invitation in the more mature age groups. We attributed this finding to a more responsible personal health attitude in these groups. The literature regarding factors that predict participation in cervical screening is inconsistent (Lockwood-Rayermann, 2004) and offers little guidance to improve on screening strategies for local circumstances.

We conclude that in a setting of a well-attended opportunistic cervical screening programme the effect of an invitation letter to nonattenders resulted in an increase in Pap smear rate of 6.4%, which is high compared with other population-based randomized studies. The cost of running a registry-based invitational programme is not more than a systematic 3-yearly invitation of all screen-eligible women irrespective of their screening status.

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References