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OPTIMIZATION OF COMPLIANCE IN EPIDEMIOLOGIC RESEARCH AND DISEASE PREVENTION

**With special emphasis on PAP-smear
screening**

by

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THE ROAD TO WISDOM

The road to wisdom? - Well, its plain
and simple to express:

Err
and err
and err again
but less
and less
and less.

Grooks, by Piet Hein

To Christer, Malin and Sara

SUMMARY

The aim of this thesis was to investigate factors affecting attendance in screening for cervical cancer, and to evaluate various measures aimed at increasing compliance to self-administered postal questionnaires and screening for cervical cancer.

A population-based randomized controlled trial including 2000 men and women aged 20-79 years and living in Sweden was conducted to investigate compliance to postal questionnaires. In a randomized 2³ factorial design three factors were tested: 1) preliminary notification or not, 2), questionnaire length, and 3) mention of a possible telephone contact or not.

Preliminary notification increased the response rate by 7%, a short questionnaire with 5%, whereas mention of a possible telephone contact did not influence attendance. Combinations of preliminary notification and short questionnaires increased the response rate by 16%, whereas young age, male gender and urban residence lowered the response rate.

The relation between non-attendance to screening for cervical cancer (Pap smear screening) and sociodemographic factors, gynecological examinations, risk behavior, general health behavior, knowledge, attitudes and beliefs was investigated in a population-based case-control study with 430 non-attenders and 514 attenders at Pap smear screening in Uppsala county.

Non-attendance was more likely among women who had *not* used oral contraceptives, who had *not* taken their own initiative to a Pap smear, who had visited different gynecologists, and who had visited a physician very often or not at all. Regular condom use, living in rural/semi-rural areas, and *not* knowing the recommended screening interval were all associated with non-attendance, whereas socioeconomic status was not, when tested in a multivariate model.

Multivariate analysis also showed that non-attendance was more likely among women who did *not* perceive cervical cancer to be as severe as other malignancies, who did *not* perceive the benefits of a Pap smear, who had time-consuming and economical barriers, and who did *not* feel anxious about the test results or cervical cancer. The results were strengthened with increasing time since the last smear or if self-reported attendance status was used instead of true attendance.

Non-attenders also kept holding on harder to their preferences than did attenders, stating that they would not participate if their preferences were not met and were less likely to intend to participate in future screening. Among the non-attenders, 57% underestimated the time lapse since the last smear.

Modifications of the invitation and call-recall system for Pap smear screening was investigated in a randomized controlled trial including all 12,240 women invited to organized screening during 17 weeks in 2001 in Uppsala County. Three successive interventions were tested: 1) modified invitation vs. the standard invitation letter, 2) reminder letter vs. no reminder letter, and 3) phone reminder vs. no phone reminder.

Whereas the modified invitation did not increase attendance, a reminder letter increased the proportion attending by 9%, and a phone reminder by 31%. Combinations of modified invitation, written reminder and phone reminder almost doubled attendance within 12 months, and the number of detected cytologic abnormalities was more than tripled.

CONTENTS

List of papers.....	iv
Abbreviations and definitions.....	v
1 Introduction	1
1.1 Compliance in epidemiological studies.....	1
1.2 Compliance at screening for cervical cancer	1
2 Background.....	3
2.1 Compliance in epidemiological studies.....	3
2.1.1 Increasing response rate to postal questionnaires	3
2.2 Compliance at screening for cervical cancer	5
2.2.1 Cervical cancer	5
2.2.2 Screening for cervical cancer	9
2.2.3 Factors affecting attendance at Pap smear screening	10
2.2.4 Increasing attendance at Pap smear screening.....	15
3 Aims.....	17
4 Material and methods.....	18
4.1 Data sources	18
4.1.1 The National Population Register	18
4.1.2 The Cytology Register in Uppsala County	18
4.1.3 LOUISE Register.....	18
4.1.4 The Swedish Cancer Register	18
4.2 Paper I.....	19
4.2.1 Study design and subjects.....	19
4.2.2 Interventions and randomization.....	19
4.2.3 Statistical methods	20
4.3 Paper II-III.....	20
4.3.1 Definition of non-attenders	20
4.3.2 Study design and subjects.....	20
4.3.3 Data collection	21
4.3.4 Statistical methods	23
4.4 Paper IV.....	24
4.4.1 Study design and subjects.....	24
4.4.2 Interventions and randomization.....	24
4.4.3 Statistical methods	27
5 Results.....	28
5.1 Paper I.....	28
5.1.1 Demographic characteristics	28
5.1.2 Interventions	28
5.1.3 Partial non-response	29
5.2 Paper II-III.....	30
5.2.1 Validity of self-reports (Paper II).....	30
5.2.2 Demographic and socioeconomic factors (Paper II-III).....	31
5.2.3 Risk behavior and gynecological history (Paper II)	31

5.2.4	Health behavior and health status (Paper II).....	32
5.2.5	Information and knowledge (Paper II)	32
5.2.6	Attitudes and beliefs (Paper III)	34
5.2.7	Preferences and future intentions (Paper III)	36
5.3	Paper IV	39
5.3.1	Baseline characteristics.....	39
5.3.2	Interventions.....	39
5.3.3	Cumulative effects	41
6	General discussion	43
6.1	Methodological considerations	43
6.1.1	Study design	43
6.1.2	Precision	43
6.1.3	Validity	44
6.2	Interpretations and Implications of findings.....	48
6.2.1	Increasing response rate to postal questionnaires (Paper I).....	48
6.2.2	Factors affecting attendance at Pap smear screening (Paper II-IV) .	50
6.2.3	Increasing attendance at Pap smear screening (Paper IV).....	56
6.3	Implications for future research	58
6.3.1	Interventional strategies.....	58
6.3.2	Additional questions	59
7	Conclusions.....	61
8	Acknowledgements	62
9	References.....	64

LIST OF PUBLICATIONS

This thesis is based on the following papers, which will be referred to in the text by their Roman numerals:

- I. Eaker S, Bergström R, Bergström A, Adami HO, Nyren O: Response rate to mailed epidemiologic questionnaires: A population-based randomized trial of variations in design and mailing routines.
Am J Epidemiol 1998; 147:74-82.
- II. Eaker S, Adami H-O, Sparén P. Reasons why women do not attend screening for cervical cancer. A population based study in Sweden.
Prev Med 2001 Jun; 32(6):482-91.
- III. Eaker S, Adami HO, Sparén P. Attitudes to screening for cervical cancer. A population based study in Sweden.
Cancer Causes & Control 2001; 12:519-28.
- IV. Eaker S, Adami HO, Granath F, Wilander E, Sparén P. Intervention to increase attendance at screening for cervical cancer. A large population-based randomized controlled trial in Sweden.
Submitted.

LIST OF ABBREVIATIONS AND DEFINITIONS

CI	Confidence interval
CIN	Cervical intraepithelial neoplasias
	CIN 1 Mild or moderate dysplasia
	CIN 2 Severe dysplasia
CIS	CIN 3 Carcinoma <i>in situ</i>
DNA	Deoxyribonucleic acid
HBM	Health Belief Model
HPV	Human papillomavirus
OC	Oral Contraceptive
OR	Odds Ratio
Pap	Papanicolaou

1 INTRODUCTION

In both epidemiological research and disease prevention, compliance is essential for a successful outcome. In epidemiological studies, participation by answering questions about living habits (such as smoking and diet) and other important environmental factors provides a basis for discerning the causes of different illnesses with an eye to eventual prevention. As regards preventive care, participation is obviously a prerequisite for prevention. It does not matter how important an investigation is or how well a preventive measure is designed if people are not willing to participate.

The goals of this investigation were therefore to illuminate reasons for non-compliance in Pap smear screening as well as to evaluate various measures aimed at increasing compliance to postal questionnaires and Pap smear screening.

1.1 COMPLIANCE IN EPIDEMIOLOGICAL STUDIES

Mailed questionnaires are standard tools in epidemiological research because questionnaire studies are less time-consuming than telephone- and personal interviews, they are free from the influence of interviewers and are relatively cheap. The mail responses may also be more valid than responses from other data collection methods (Siemiatycki et al., 1984), which may be related to the time available to consider the questions. However, mailed questionnaires often have a lower response rate than telephone- and personal interviews (Yu et al., 1983). A high response rate may be of critical importance for validity and cost efficiency. A low rate may cause selection bias in case-control studies and undermine the follow-up in prospective studies. Although several studies in sociology and marketing research have evaluated factors that may affect the response rate positively, comparatively little effort has been devoted to studying technical aspects of the administration of mailed epidemiological questionnaires.

To evaluate various measures taken to increase compliance, we conducted a population-based randomized controlled trial including 2000 men and women in Sweden.

1.2 COMPLIANCE AT SCREENING FOR CERVICAL CANCER

Cervical cancer, the second most common malignancy globally among women (Parkin et al., 2001), is also potentially one of the most preventable (Ponten et al., 1995). The use of cervical Papanicolaou (Pap) smears can markedly reduce mortality and suffering from cervical cancer (Ries et al., 1999; Vizcaino et al., 2000). Since cervical cancer afflicts relatively young women, its effect on cancer-related reduction of life span is considerable (National Board of Health and Welfare, 2002:4). In Sweden, the introduction of Pap smear screening about three decades ago resulted in removal of precursor lesions on a large scale, which ultimately reduced the national incidence of invasive cancer by about 50 percent (Bergstrom et al., 1999; Gustafsson et al., 1990). However, epidemiological studies (IARC Working Group on evaluation of cervical cancer screening programmes, 1986) and mathematical modeling (Gustafsson et al., 1992) indicate that a much larger reduction would be within reach if compliance with the screening program were improved. Most

cervical cancers occur in women who have had few or no smear tests at all (Gillam, 1991; Janerich et al., 1995), and cervical cancer is most common in countries without an established screening program, where large parts of the population have not had a Pap smear (Parkin et al., 1999:a). In settings where all women have access to cervical cancer screening, one main reason for disease occurrence seems to be non-compliance. Although women usually favor the idea of having a Pap smear, they do not always apply it to themselves (Elkind et al., 1988). Comparatively little research has been devoted to investigating why so many women do not participate in screening for cervical cancer. Prior studies have often been limited in size, been restricted to certain groups or have based attendance status on the women's self-reported screening only.

To investigate reasons for non-compliance at Pap smear screening, we conducted a population-based case-control study, taking advantage of the extraordinary prerequisites afforded by a computerized register covering all smears taken in Uppsala County in Sweden during 30 years. This register allowed a large population-based study with complete information on each woman's screening history.

To evaluate various measures taken to increase compliance at Pap smear screening, we conducted a large-scaled population-based randomized controlled trial including all women in Uppsala County who were due for Pap smear screening during a period of four months (12,240 women). To our knowledge, no prior population-based randomized controlled trial conducted on a large sample of women of all ages relevant for screening has been done.

2 BACKGROUND

2.1 COMPLIANCE IN EPIDEMIOLOGICAL STUDIES

There are large differences in response rate depending on the method used to collect data from the participants. The highest response rates have been generated by using personal interviews and telephone interviews (around 80% and 70%, respectively) (Yu et al., 1983), whereas postal questionnaires have generated the lowest response rates (between 45-50%) (Heberlein et al., 1978; Kalantar et al., 1999; Yu et al., 1983). The response rate of an investigation is, however, also dependent on a number of other factors, such as the topic and population investigated, and it can be increased by a number of manipulative strategies.

2.1.1 Increasing response rate to postal questionnaires

Most of the studies evaluating factors that may affect the response rate positively have been conducted in sociological and marketing research. In these research areas the effects of several possible manipulations have been investigated, such as the effects of preliminary notification (Fox et al., 1988; Harvey, 1987; Linsky, 1975; Yammarino et al., 1991; Yu et al., 1983) and length of the questionnaire (Dillman, 1978; Harvey, 1987; Linsky, 1975; Yammarino et al., 1991; Yu et al., 1983). Epidemiological studies may be perceived by the public as particularly important, but their questions are often complex and may be difficult to answer. Therefore, the response pattern in such studies may not be directly inferred from research in other areas. Prior epidemiological studies on these matters have generally been performed in highly selected groups of individuals (Kelsey et al., 1989; Kuskowska-Wolk et al., 1992; Spry et al., 1989) and have dealt mainly with the importance of demographic factors, such as age (Kelsey et al., 1989), gender and urban dwelling (Marrett et al., 1992) – factors that cannot be manipulated to improve the response rate. Comparatively little effort has been devoted to studying technical aspects of the administration of mailed epidemiological questionnaires. Exceptions are studies dealing with the effects of reminders and economic incentives to the participants (Marrett et al., 1992; Perneger et al., 1993; Spry et al., 1989; Tambor et al., 1993) and of various types of stamps on return envelopes (Choi et al., 1990).

Despite differences (in area of research, design, topic, etc.) between prior studies, a number of broad strategies to increase compliance seem to be of special interest and importance. Since studies of the effects of possible manipulations to increase response rate in medical surveys are too sparse, the results now presented mainly come from studies conducted in sociology and marketing research.

2.1.1.1 Topic, how it concerns the participant and personalization

The topic of the investigation and a feeling of making a contribution are important for compliance. In one study, an 11% higher response rate was reached when the word “cancer” was used in the contact letter rather than the more general “health study” (Walter et al., 1988:a), and in another study an 10% higher response rate was observed when “Women and Cancer” was used as a heading instead of “Oral Contraceptives and Cancer” (Lund et al., 1998). Moreover, the perceived importance of the study in preventing a disease is an important factor in motivating response (Savitz et al., 1986;

Taylor et al., 1991). Questionnaires originating from universities have also been found to be more likely to be returned than are questionnaires from other sources, such as commercial organizations (Edwards et al., 2002; Fox et al., 1988).

How the topic concerns the participants is associated with the motivation to respond. It is common knowledge, at least in medical research, that the response rate is lower among controls in a case-control study about disease. As an example, in one study the highest baseline response rate was reached among cases with cancers with a median survival rate of four years or more (from 81% to 87%), whereas the lowest response rates was reached among the population controls (64%) (Parkes et al., 2000). A feeling of lack of personal benefit from responding has also been found to be a main reason for non-compliance (Bakke et al., 1990) and a higher response rate has been reached when the questionnaires were designed to be of more interest to the participants (Edwards et al., 2002; Lund et al., 1998).

The response rate also increases if a personalized questionnaire (as opposed to anonymity) and letter are used (Edwards et al., 2002; Linsky, 1975; Yu et al., 1983), whereas no effect of anonymity has been observed (Campbell et al., 1990)

2.1.1.2 Prior contact, reminders, and length

Contacting the participants beforehand (Edwards et al., 2002; Fox et al., 1988; Harvey, 1987; Linsky, 1975; Spry et al., 1989; Yu et al., 1983), as well as using reminders (Edwards et al., 2002; Fox et al., 1988; Linsky, 1975; Perneger et al., 1993; Salim Silva et al., 2002; Spry et al., 1989; Tambor et al., 1993; Yammarino et al., 1991; Yu et al., 1983) has been found to increase the response rate to postal questionnaires. Prior contact and reminders, both by phone, seem to be the most effective method (Hoffman et al., 1998)

The impact of questionnaire length has been widely examined (Edwards et al., 2002; Harvey, 1987; Hoffman et al., 1998; Kalantar et al., 1999; Linsky, 1975; Lund et al., 1998; Spry et al., 1989; Yammarino et al., 1991; Yu et al., 1983). However, the results are ambiguous, and both positive and negative effects, as well as no effect at all of cutting pages in the questionnaire are reported. In one study (Yu et al., 1983), the highest response rate was reached using questionnaires with 41-50 items, whereas questionnaires either with more or fewer items had a lower response rate (Yu et al., 1983).

2.1.1.3 Incentives and postage

The possible effect on the response rate of using different kinds of incentives has also been extensively investigated in both marketing research and in medical surveys. Monetary incentives have been found to increase the response rate in many (Edwards et al., 2002; Halpern et al., 2002; Linsky, 1975; Parkes et al., 2000; Perneger et al., 1993; Spry et al., 1989; Tambor et al., 1993; Yammarino et al., 1991; Yu et al., 1983), but not all (Fox et al., 1988) investigations. Even non-monetary incentives, such as key rings and lottery tickets, may have a slight effect on the response rate (Edwards et al., 2002; Kalantar et al., 1999; Spry et al., 1989; Yu et al., 1983). The effects of incentives have, however, also been shown to decrease (Kalantar et al., 1999), or even disappear (Marrett et al., 1992; Spry et al., 1989) after repeated follow-ups.

Sending the questionnaire by registered mail or first class mail have also been shown to increase the response rate (Edwards et al., 2002), as did using a stamped return envelope (Yammarino et al., 1991), especially if paper stamps were used (Choi et al., 1990).

2.2 COMPLIANCE AT SCREENING FOR CERVICAL CANCER

In the 1940s, George Papanicolaou discovered shedding of atypical cells in women who did not yet have invasive cervical cancer (Papanicolaou, 1948), thereby providing a tool by which asymptomatic precursor lesions to cervical cancer could be detected. Thus was the Pap smear invented. The precursor lesions can be removed by a simple procedure (usually through laser conization) and thereby their progress into cervical cancer is prevented. Hence, the use of Pap smear screening can markedly reduce the occurrence of, and death from, cervical cancer. The precursor lesions are asymptomatic and can only be detected by a Pap smear. When symptoms appear, invasive cervical cancer has already developed. It is estimated that Pap smears every third year can prevent 90% of all cervical cancers in a population where all women attend and all detected lesions are adequately followed-up (IARC Working Group on evaluation of cervical cancer screening programmes, 1986).

Recent development of the HPV (Human Papillomavirus) DNA test might improve screening, and vaccination against oncogenic HPV types might further improve the prevention of cervical cancer. However, independent of the method of prevention, compliance is central.

2.2.1 Cervical cancer

The lower third of the uterus is called the cervix (Figure 1), which partly extends into the vagina. This is the place where cervical cancer occurs.

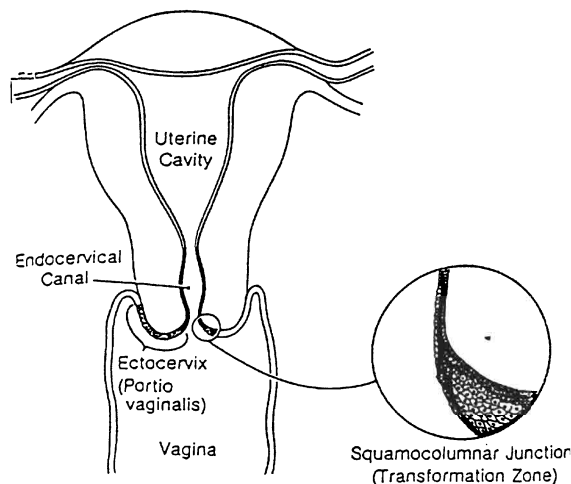


Figure 1

2.2.1.1 Natural history of cervical cancer

To be suitable for control by a program of early detection and treatment, a disease must pass through a preclinical phase during which it is undiagnosed but detectable, and earlier treatment must offer some advantage over later treatment (Cole et al., 1980; Morrison, 1992). Cervical cancer provides one of the best examples of the natural history of a disease suitable for screening due to its gradual development from precursor lesions to invasive cervical cancer and since the precursor stages to the disease can be detected long before cancer develops.

Cervical cancer gradually develops from dysplasia (CIN 1-2), through carcinoma *in situ* (CIS), asymptomatic invasive cancer and finally symptomatic invasive cancer. The most common classification used to describe this is a histologically-based classification system proposed by Richart in the mid 1960s (Richart, 1966). According to this system, the epithelial neoplastic changes evolve through a morphological and biological continuum of progressive stages; namely, cervical intraepithelial neoplasias (CIN) 1 (mild or moderate dysplasia), CIN 2 (severe dysplasia) and CIN 3 (which is morphologically indistinguishable from cervical carcinoma *in situ* (CIS) (Figure 2).

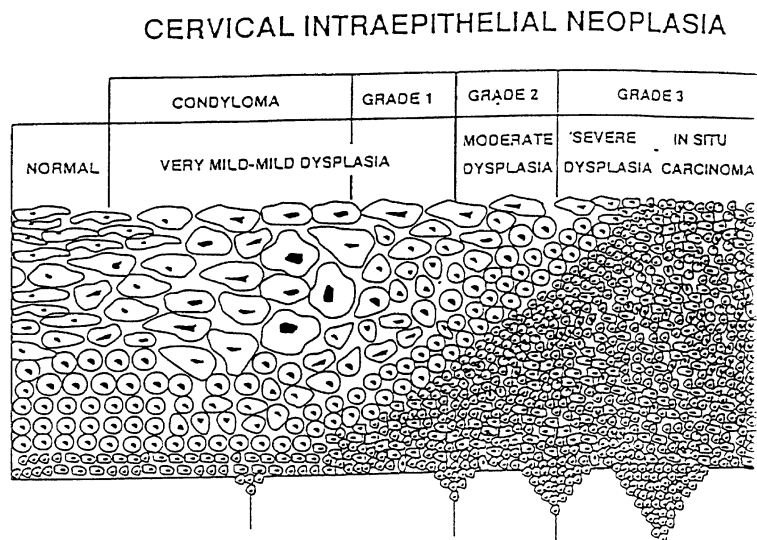


Figure 2

In about 11% of the women with mild dysplasia (CIN 1) it will progress into cervical carcinoma *in situ* (CIS) if left untreated, whereas in 32% it will persist and in 57% it will regress (Östör, 1993). Perhaps less than 20% of CIN 3 will progress into cervical cancer (Ponten et al., 1995). Therefore, a fairly small proportion of the precursor stages have the potential to progress into invasive cervical cancer. However, since it is not clear in which individuals the precursor stages will progress over-treatment of these stages occur. In a population that does not undergo screening, the majority of affected women will seek medical care in a late stage (when symptoms appear) when no cure can be obtained. The over-treatment is thus the price to pay for the benefit of intervention. Cervical cancer usually progresses slowly, and the time for progression from carcinoma *in situ* to clinically detectable invasive cancer has been estimated at about 17 years, the *in situ* stage covering 13 years and the pre-clinical invasive stage 4 years (Gustafsson et al., 1989).

There are three types of cervical cancer; namely, squamous-cell carcinoma, adenocarcinoma and adeno-squamous carcinoma. Squamous-cell carcinoma is the predominant type (around 80% of all cervical cancers in Sweden) and is preventable by Pap smear screening. Hitherto, no evidence exist that the Pap smear has a preventive effect on adenocarcinoma (around 20% of all cervical cancers) or adeno-squamous cancer (1-2% of all cervical cancers) (Bergstrom et al., 1999).

Cervical cancer affects relatively young women, and in populations with no established screening, the age-specific incidence rate shows a steep rise from the age 20-25, a peak

at 45-50 and then a modest decline in later years (Sparen et al., 1995). In screened populations, as in Sweden today, the incidence tends to be highest among women above the age of 60 years (Gustafsson et al., 1997).

2.2.1.2 Incidence of cervical cancer

Cervical cancer is not only the second most common cancer in women, it is also the second main cause of death from cancer in women, and in many developing countries the most common (Parkin et al., 2001). The world incidence was estimated at 470,000 cases during the year 2000, accounting for 9.9% of all new cancer cases among women (<http://www-dep.iarc.fr/globocan/globocan.html>), and this cancer type causes 233,000 deaths annually (Parkin et al., 2001). Cervical cancer is more common in developing countries, where almost 80% of the cases occur and where cervical cancer accounts for 14.8% of female cancer, whereas it accounts for only 4.2% of new cases in developed countries (<http://www-dep.iarc.fr/globocan/globocan.html>). The great differences in incidence rates of invasive cervical cancer between populations are mainly due to differences in etiological environmental factors between settings and the possibility to use screening. The highest incidence rates are observed in Latin America and the Caribbean, sub-Saharan Africa, and South- and Southeast Asia, with age-standardized incidence rates over 35.5 per 100,000 women. The lowest rates are observed in China, Western Asia, as well as certain countries in Europe (such as Luxemburg and Finland) with incidence rates below 9.3 per 100,000 women (Bray et al., 2002; Parkin et al., 2001).

Cervical cancer is one of the few malignancies that show a marked reduction in incidence and mortality over the past decades. The reduction is most clearly observed in the western countries where well-developed screening programs exist (IARC Working Group on evaluation of cervical cancer screening programmes, 1986; Parkin et al., 1999;b; Vizcaino et al., 2000).

In Sweden, the number of cases of cervical cancer has shown a drastic decrease in incidence since the screening program was introduced in the mid 1960s (Bergstrom et al., 1999; Gustafsson et al., 1990). In 1960, a total of 783 women were diagnosed with cervical cancer, and the age-standardized incidence rate (according to the population in Sweden 2000) was 21.3 per 100,000 women. In the mid 1960s, the incidence started to decline. In 1980, the age-standardized incidence rate was 12.6 per 100,000 women (524 cases) (<http://www.sos.se/epc/stat/cancreg.htm>), and in 2000 only 9.7 per 100,000 women (450 cases), accounting for only 2.0% of female cancer (National Board of Health and Welfare, 2002:5). The mortality has also declined in the same manner (National Board of Health and Welfare, 1998).

2.2.1.3 Etiology (study of risk factors for cervical cancer)

Established or proposed risk factors for cervical cancer include infection by HPV, low socioeconomic status, race (black and Hispanic), multiparity, early age at first intercourse, large number of sexual partners, male partner with many sexual partners, smoking, oral contraceptive use, diet poor in fruit, vegetables and some micronutrients, other sexually transmitted agents and immunosuppression (Ponten et al., 1995; Ylitalo, 2000).

Certain types of HPV (notably types 16, 18, 31 and 45) are considered to be a necessary (but not sufficient) cause of cervical cancer (Munoz et al., 2003). HPV infection is a common sexually transmitted disease, and although most infections are benign, some progress to cancer. It has been estimated that 99.7% of the invasive cervical cancers worldwide contain HPV, which implies that HPV is the highest worldwide attributable fraction so far reported for a specific cause of any major human cancer (Walboomers et al., 1999).

Recent developments of a HPV DNA-test and vaccine against oncogenic HPV types (testing of this vaccine is in progress) may improve the prevention further. The recent development of an HPV DNA-test by which women with persistent infection (who constitute a high-risk group) can be identified, should allow focused surveillance by regular screening. A vaccine against oncogenic HPV types, which is now undergoing clinical testing (Koutsky et al., 2002), may eventually be useful for preventing cervical cancer.

Cervical cancer has been found to be more common among women with low socioeconomic status (measured by income and education), something that may be a reflection of differences in smoking habits and sexual behavior between social groups (Ponten et al., 1995; Ylitalo, 2000). Another reason could be that many women with low socioeconomic status fail to obtain the necessary follow-up and treatment for their abnormal Pap smear (Michielutte et al., 1994). The risk of cervical cancer is higher among blacks and Hispanics, something that, in part, may be explained by the close relationship between race and socioeconomic status in many countries. Both early age at first intercourse, large number of sexual partners and a male partner with many sexual partners are risk factors for cervical cancer, probably due to a higher exposure to HPV infections. Multiparity, on the other hand, is considered as an HPV-independent risk factor for cervical cancer, and may be explained by numerous factors connected with pregnancy (such as hormonal influence).

As with many other cancer forms, and many other diseases, smoking (especially current, long-term and high-intensity smoking) is associated with an increased risk of cervical cancer. Oral contraceptive (OC) use, particularly current and long-term, may also be a risk factor for cervical cancer, although the effects of OC use have been hard to evaluate due to its close relationship with sexual history (and thus HPV infection) and cytological screening (Ponten et al., 1995; Ylitalo, 2000). However, some studies do indicate that OC use may be an HPV-independent risk factor for certain types of cervical cancer (Lacey et al., 1999; Moreno et al., 2002). Certain vegetables and fruits (containing beta-carotene, vitamin A and C and folate) may be protective against cervical cancer, whereas other sexually transmitted agents, such as herpes simplex virus 2 (HSV-2) and a chlamydia trachomatis infection, have been considered as potential risk factors for cervical cancer (Ponten et al., 1995; Ylitalo, 2000). In recent studies, chlamydia trachomatis infection was associated with subsequent development of cervical cancer (Anttila et al., 2001), whereas HSV-2 either was not (Lehtinen et al., 2002), or was suggested to act in conjunction with HPV infection to increase the risk of invasive cervical cancer (Smith et al., 2002). Immunosuppression (among women with HIV and among renal transplant recipients), has also been associated with an increased susceptibility to HPV infection and thereby a higher risk of cervical cancer (Ponten et al., 1995; Ylitalo, 2000).

2.2.2 Screening for cervical cancer

Screening can be defined as an examination of asymptomatic persons in order to classify them as likely or unlikely candidates for the disease that is the object of screening, and the goal of screening is to reduce morbidity or mortality from that disease by early treatment of the cases discovered (Morrison, 1998).

2.2.2.1 *Organized and Opportunistic screening*

Screening for cervical cancer can be either organized or opportunistic. In an organized screening program, women of certain ages (usually from 20-30 to 50-60 years of age) are invited to screening at regular intervals. In opportunistic screening the initiative to have a Pap smear is taken by the woman herself or by her physician, for example, when visiting a gynecologist for another reason. There are no great differences in efficiency between organized and opportunistic screening in the detection of carcinoma *in situ* (Gustafsson et al., 1995:b), although the overall coverage is greater when an organized program is introduced (Nygard et al., 2002). A difference in the efficiency of detecting cervical cancer may, however, exist (Nieminen et al., 1999). A possible explanation for this may be that past screening patterns differ between women attending organized and opportunistic screening.

Today, opportunistic screening for cervical cancer exists in most developed countries, whereas nationwide organized programs exist only in few of them (as in Sweden, Finland, Iceland, Norway, the Netherlands, the United Kingdom, large parts of Canada, Italy, and Japan). In most developing countries, no resources for screening exist, and in 1986 it was estimated that less than 5% of the women had been screened within the previous five years (WHO, 1986).

2.2.2.2 *Screening in Sweden*

In Sweden, screening for cervical cancer began on a limited scale in 1961, whereas a nationwide organized program was introduced in 1967 through 1973 (except for the city of Gothenburg, where an organized screening program was not in effect until 1977) (National Board of Health and Welfare, 1976). Initially, all women aged 30 to 49 years were invited to screening every 4th year, but later, this age interval was expanded and the screening interval shortened to 3 years (some variations exist between different counties). The recommended screening interval is, for women aged 23-50, every third year, and for women 51-60 every fifth year (National Board of Health and Welfare, 1998). The annual number of smears (in both organized and opportunistic screening) since 1970 has been almost 1 million, of which around 30% are taken within the organized screening (National Board of Health and Welfare, 1998).

2.2.2.3 *Screening in Uppsala County*

In Uppsala County, where our studies were conducted (Paper II-IV), an organized program was introduced in 1967. Initially, the organized screening was run independently of opportunistic screening, but since 1972 only women with no registered smear (in either organized or opportunistic screening) were invited every 3-4 years (Gustafsson et al., 1995:a). Since 1998, women aged 25-59 years have been invited for screening every 3rd year. The Pap smears in the organized program are taken free

of charge or at a low cost, by specially trained midwives. Around 20% of the Pap smears are taken in the organized screening and the rest in opportunistic screening, that is, by gynecologists or private midwives (Gustafsson et al., 1995:b).

Most women in Sweden have at some time had a Pap smear. However, around 70% of the women in Uppsala County do not attend after an invitation to organized screening and many have not had a Pap smear during a long time period. In 1996, 41% of the women aged 25-29 and 55-59, and 35% of the women aged 30-54 years, had not had a Pap smear during the previous 3 years, and between 20-25% of women aged 30-59 years not within the previous five years (Pär Sparén – personal communication).

2.2.3 Factors affecting attendance at Pap smear screening

In the late 1980s and during the 1990s several studies investigated why not all women attend Pap smear screening. Many of them were, however, based on small samples or highly selective groups or focused on selective issues (Doyle, 1991; Eklund et al., 1988; Hesselius et al., 1975; Naish et al., 1994; Nathoo, 1988). Furthermore, many studies have based the women's attendance status on self-reports only (Katz et al., 1994; Lantz et al., 1997; Murray et al., 1993:a), something that has been shown to be unreliable (Paskett et al., 1996; Suarez et al., 1995; Walter et al., 1988:b). In some studies a partial validation of self-reports was possible, either through access to physician's records (Peters et al., 1989) or computerized databases covering organized, but not opportunistic, screening (Ciatto et al., 1991; Elkind et al., 1988; Hesselius et al., 1975).

Large differences in design, individuals selected, definition of a non-attender, statistical analysis, and the possibility to verify attendance status exist among prior studies. Furthermore, many of the studies have been conducted either in settings without an established organized screening program (such as in the United States), or where the organized screening program was in an early stage.

2.2.3.1 Demographic and socioeconomic factors

Several studies indicate that both younger women (younger than 30-34 years) (Berrino et al., 1979; Hesselius et al., 1975; Orbell et al., 1996:a; Orbell et al., 1995), and especially older women (over the age of 50-60 years) (Bergmann et al., 1996; Berrino et al., 1979; Calnan, 1985; Mandelblatt et al., 1999; Maxwell et al., 2001; Nicoll et al., 1991; Orbell et al., 1996:a) are more likely to be non-attenders at Pap smear screening. Explanations given as to why older women have a lower attendance rate are negative attitudes towards the examination and the belief that that area of their bodies is uninteresting after menopause (King, 1987).

Women living in rural areas have been found to be less likely to have attended Pap smear screening (Katz et al., 1994), as have ethnic minorities (Seow et al., 2000) and immigrants (Harlan et al., 1991). Reasons may be cultural differences in attitudes towards cervical cancer and perceived susceptibility (Chavez et al., 1997; Hubbell et al., 1996; Mandelblatt et al., 1999; Yi, 1998), and language barriers and the duration of residency in the new country for immigrated women (Kernohan, 1996; Naish et al., 1994; Peters et al., 1989).

Women who are single have also been found to be less likely to have attended Pap smear screening (Bergmann et al., 1996; Berrino et al., 1979; Hesselius et al., 1975; Lantz et al., 1997;

Maxwell et al., 2001; Murray et al., 1993:a; Nicoll et al., 1991; Orbell et al., 1995), as have women with no children (Hesseliuss et al., 1975; Nicoll et al., 1991). Others studies found no relationship after controlling for confounding factors (Paskett et al., 1996; Peters et al., 1989), such as knowledge about the screening interval, barriers to attend, and contact with the medical health care system during pregnancy (Peters et al., 1989).

Since women with low socioeconomic status have a higher risk for cervical cancer (Vagero et al., 1986), this has been one of the most investigated determinants of screening attendance. In several studies, educational level, income and insurance were important predictors for non-attendance, since women with low education (Ciatto et al., 1991; Hewitt et al., 2002; Katz et al., 1994; Maxwell et al., 2001; Segnan, 1997), low income (Hewitt et al., 2002; Katz et al., 1994; Segnan, 1997), and with no medical insurance (Hewitt et al., 2002; Katz et al., 1994; Kottke et al., 1995; Lantz et al., 1997; Segnan, 1997) were more likely to be non-attenders. A few studies show that these factors are merely indicators for more powerful predictors of attendance (Lantz et al., 1997; Murray et al., 1993:b; Paskett et al., 1996; Katz, 1994 #161; Peters et al., 1989), predictors that are distributed unevenly among the subgroups of women. In one study, the presence or absence of universal insurance coverage did not predict non-attendance among women with low incomes (Katz et al., 1994), and in other studies the effects of education and income were explained by knowledge, use of oral contraceptives, number of pregnancies and immigration (Peters et al., 1989), or were mediated by health beliefs and aversive views about the test and its results (Orbell, 1996:b; Orbell et al., 1996:a).

2.2.3.2 Risk behavior and gynecological history

Neither smoking nor sexual risk behaviors, such as age at first intercourse and the number of sexual partners, seem to predict non-attendance (Ciatto et al., 1991; Orbell et al., 1995; Peters et al., 1989). On the contrary, screened women have even reported to have had more sexual partners (Orbell et al., 1996:a), and sexually active women to be more likely to intend to obtain a pelvic exam (McKinley et al., 1998). One study also found that women with a sexual risk behavior perceive themselves as at higher risk and to a greater extent feel that participation would give them peace of mind (Orbell et al., 1996:a).

Other variables that have been shown to reduce compliance to screening are low frequency of gynecological examinations for other reasons, such as for infections or prescriptions for oral contraceptives (Calnan, 1985; Peters et al., 1989), and the lack of a regular physician or a gynecologist (Ciatto et al., 1991; Lantz et al., 1997) or other health care source (Mandelblatt et al., 1999).

2.2.3.3 Health behavior and health status

The effect of perceived health status and health-related behavior on attendance at Pap smear screening has only been investigated in a few studies. In one study, perceived health status had no effect on attendance (Calnan, 1985) and in another study it went in two directions, depending on age (Mandelblatt et al., 1999). Younger women in good health were more likely to be non-attenders, as were older women in poor health (Mandelblatt et al., 1999). Health-related behavior, such as attending mammography and conducting breast self-examination, were positively associated with attendance at Pap smear

screening in some studies (Calnan, 1985; Murray et al., 1993:a), whereas others have found no such association (Ciatto et al., 1991).

2.2.3.4 Information and knowledge

It has been reported that around 50% of all women consider that insufficient information about cancer, or about the Pap smear, is given by the doctors (Hesselius et al., 1975; Nicoll et al., 1991). Many women also find it difficult to understand the information given, since it is too technical (Kavanagh et al., 1997). In one study, non-attendance was also more common among women who feel that they have received insufficient information from their doctor (Ciatto et al., 1991; Larsen et al., 1998).

Overall, in several studies, the women's knowledge about the Pap smear and cervical cancer are reported to be poor. Many women do not know which cancer type the Pap smear is intended to prevent (Berrino et al., 1979; Hesselius et al., 1975; Nicoll et al., 1991), or believe that the main purpose of the test is to detect existing cancer (Fylan, 1998). Women with detected abnormality may also assume that they have cancer, not knowing that the smear test detects precursor lesions (Kavanagh et al., 1997). Knowledge may also influence attendance, i.e., women having poor knowledge about the purpose of screening (Ciatto et al., 1991; Foxwell et al., 1993; Hesselius et al., 1975; Nicoll et al., 1991) or the recommended screening interval (Peters et al., 1989) may be more likely to be non-attenders. Women also seem to have poor knowledge about the risk factors for cervical cancer (Fylan, 1998; Kowalski et al., 1994; Price et al., 1996).

Knowledge about the Pap smear and risk factors may be age-dependent. Although older women (40-59 years) have better knowledge than young women (20-39 years) about which type of cancer the screening is actually for (Idestrom et al., 2002), younger women seem to have a better knowledge about the risk factors for the disease (King, 1987; Kowalski et al., 1994; Neilson et al., 1998).

2.2.3.5 Attitudes and beliefs

Several studies have investigated the effect of attitudes, beliefs and anxiety on compliance at Pap smear screening. As others have done (Burak et al., 1997; Hill et al., 1985; King, 1987; Murray et al., 1993:b; Orbell et al., 1996:a; Orbell et al., 1995; Price et al., 1996; Seow et al., 1995), we based several of our questions about attitudes and beliefs on the Health Belief Model (HBM).

2.2.3.5.1 The Health Belief Model

Several theoretical models aim to explain health behavior, such as the Transtheoretical Model and Stages of Change, the Theory of Reasoned Action and the Theory of Planned Behavior, the Health Locus of Control, and the Health Belief Model (Strecher et al., 1996).

Initially developed by Irwin Rosenstock (Rosenstock, 1974), the Health Belief Model (HBM) is among the most widely used psychosocial approaches to explain health-related behavior (Strecher et al., 1996). The HBM is a value expectancy model (cognitive model), gradually reformulated to explain health-related behavior (Strecher et al., 1996).

The HBM postulates that the likelihood that an individual will engage in a given health behavior is a function of subjective perceptions of: (a) *perceived susceptibility*, i.e., the subjective perception of his or her risk of contracting a health disorder, (b) *perceived severity*, i.e., the subjective perception of how serious it would be to contract that disease and to leave it untreated, (c) *perceived benefits*, i.e., subjective perception of how efficient an action is in reducing either the susceptibility to or the severity of that disease, (d) *perceived barriers*, i.e., subjective perception of barriers with potentially negative aspects of a particular health action that may act as impediments to undertaking a recommended behavior, and (e) *cues-to-action* that may sometimes trigger a health behavior. The original model was, in 1977, expanded into *self-efficacy*, i.e., the belief in one's ability to carry out the recommended action (Rosenstock, 1974; Rosenstock et al., 1988; Strecher et al., 1996). Substantial empirical evidence supports the components of HBM. Conflicting results (Ogden, 2000; Strecher et al., 1996) may be due, in part, to different interpretations of how to test the model (Lauver, 1992). Criticisms against HBM have concerned the uncertainty regarding the causal relation between beliefs and behaviors, the model's emphasis on the individual and not taking the social and economic environment into consideration, as well as the absence of a role of emotional factors such as fear and denial. Elements of the HBM may, however, be well suited to predicting screening for cervical cancer (Ogden, 2000).

Perceived susceptibility is not a strong predictor of non-attendance at Pap smear screening and it seems that women in general perceive their personal susceptibility to cancer as low (Burak et al., 1997; King, 1987; Orbell et al., 1995; Price et al., 1996; Seow et al., 1995) (Idestrom et al., 2002). In one study, non-attenders were less likely to believe that they were at risk for cervical cancer or that they needed the test and also perceived their own level of risk as lower than other women of their age (Orbell et al., 1995). However, since many of these women had not had sexual intercourse it might indicate a realistic risk appraisal (Orbell et al., 1995).

Perceived severity of cervical cancer has not been found to be a predictor of compliance at Pap smear screening (Orbell et al., 1996:a; Seow et al., 1995). In general, most women believe the consequences of cervical cancer to be severe (Burak et al., 1997; King, 1987), although only a few non-attenders believed that cervical cancer is incurable (Nathoo, 1988).

Perceived benefits have, in prior research, been one of the most important predictors to explain compliance at Pap smear screening: non-attenders are less likely to expect benefits in the form of either a feeling of peace of mind after a Pap smear (King, 1987; Orbell et al., 1995) or a belief in (or understanding of) the efficiency of the test (King, 1987; Peters et al., 1989; Orbell, 1996:b #225; Seow et al., 1995). Overall, many women do, however, seem to have a positive attitude toward the test's efficiency and perceive it as effective in saving lives (Burak et al., 1997; Kottke et al., 1995; Price et al., 1996).

Several types of perceived barriers at Pap smear screening, such as economical, time-consuming and emotional barriers, have been investigated. Rarely have the same barriers, or categorizations of them, been examined in different studies, which makes it difficult to compare them. Overall, a high degree of perceived barriers has exclusively been found to reduce compliance at Pap smear screening (Hesseliuss et al., 1975; Hill et al.,

1985; King, 1987; Lantz et al., 1997; Murray et al., 1993;b; Orbell, 1996;b; Orbell et al., 1996:a; Orbell et al., 1995; Peters et al., 1989; Seow et al., 1995), especially emotional barriers, such as fear of embarrassment, or a belief that the test would be painful or unpleasant (Hesselius et al., 1975; Hill et al., 1985; King, 1987; Larsen et al., 1998; Peters et al., 1989). In many studies, perceived barriers are also the strongest predictor of non-attendance (Hill et al., 1985; King, 1987; Larsen et al., 1998; Murray et al., 1993;b; Orbell et al., 1995).

Cues-to-action may not be one of the most important factors to investigate in a Swedish setting, since all women due for a Pap smear receive an invitation to organized screening. Additional cues-to-action that may be important for attendance are recommendations by a physician or a family member, a friend, a teacher in school, media campaigns and symptoms. Physician's recommendation (Austin et al., 2002; Kottke et al., 1995; Lantz et al., 1997) and symptoms (Price et al., 1996) have also been found to be important cues-to-action in settings with no organized screening.

Since self-efficacy has been added to the HBM only recently, many researchers have not included this variable in research about compliance at Pap smear screening. Nor have we taken this variable into consideration.

2.2.3.5.2 Other important predictors of compliance

In addition to the components of the HBM, there are a few other factors that are of interest when studying compliance. These are mainly anxiety (or worry), trust in the ability of the health care system to prevent and treat cancer, social support and fatalism. Only a few studies have investigated these factors. In two studies, non-attenders were more likely to anticipate or feel anxiety (Kowalski et al., 1994; Orbell et al., 1995). In a few other studies, fear or anxiety about the test result, fear of cancer or hospital treatments and of medical treatments, unfavorable beliefs about the curability of cancer and the efficacy of treatments are expressed as reasons for non-attendance (Bergmann et al., 1996; Elkind et al., 1989; Kottke et al., 1995; Seow et al., 1995). Fear and fatalism may, furthermore, be more important in certain subgroups (Coyne et al., 1992). Social support have had a positive effect on attendance at Pap smear screening in one (Calnan, 1985), but not in another study (about compliance to mammography screening) (Schofield et al., 1994).

2.2.3.6 Preferences and Future intentions

Most women, despite attendance status, seem to prefer a female doctor (Eklund et al., 1988; Neilson et al., 1998). Women are also more likely to undergo Pap smear screening if they see a female physician (Majeed et al., 1994), particularly if she is an internist or family practitioner (Lurie et al., 1993). Other important preferences are a special clinic or their own doctor.

In general, most women perceive the Pap smear as favorable (Nicoll et al., 1991), and are willing to have a test in the future (Crombie et al., 1995; Larsen et al., 1998; Nicoll et al., 1991), although attenders seem more willing to attend in the future than non-attenders (Larsen et al., 1998; Nicoll et al., 1991).

2.2.4 Increasing attendance at Pap smear screening

A number of studies have examined strategies to increase compliance at screening for cervical cancer through increasing knowledge or by reminders (Ansell et al., 1994; Bowman et al., 1995; Buehler et al., 1997; Campbell et al., 1997; Dignan et al., 1996; Fernandez et al., 1999; Hardy et al., 1996; Hiatt et al., 2001; Kernohan, 1996; Lantz et al., 1995; Mandelblatt et al., 1993:b; Margolis et al., 1998; Mitchell et al., 1991; Paskett et al., 1998; Paskett et al., 1999; Taylor et al., 2002; Valanis et al., 2002; White et al., 1993). Most of these studies were, however, conducted in settings where no organized screening program exists (especially in the United States), and thus did not afford the same possibility to either design a study or to control for eventual confounders (Coyne et al., 1992). Furthermore, although a few studies have used a randomized design (Bowman et al., 1995; Buehler et al., 1997; Campbell et al., 1997; Hiatt et al., 2001; Lantz et al., 1995; Margolis et al., 1998; Mitchell et al., 1991; Taylor et al., 2002; Valanis et al., 2002), they were either conducted in highly selected groups of individuals or were based on small samples.

2.2.4.1 Increasing knowledge

A variety of methods have been used successfully to increase attendance by increasing knowledge, such as mail-outs (Hardy et al., 1996; Taylor et al., 2002; Valanis et al., 2002), direct contact (Ansell et al., 1994; Kernohan, 1996; Margolis et al., 1998; Taylor et al., 2002; White et al., 1993), or educational programs or media campaigns (Dignan et al., 1996; Fernandez et al., 1999; Mitchell et al., 1991; Paskett et al., 1999). Most studies were performed on subgroups of women with low attendance to screening, such as ethnical minorities (Ansell et al., 1994; Dignan et al., 1996; Fernandez et al., 1999; Kernohan, 1996; Paskett et al., 1999; Taylor et al., 2002; White et al., 1993), low-income women (Fernandez et al., 1999; Hardy et al., 1996; Paskett et al., 1999) or women attending appointments at a certain clinic/hospital (Margolis et al., 1998). This, as well as the different methods used to increase knowledge, precludes direct comparisons between different studies as well as generalization to other settings. An overall estimate is that increased knowledge can be a powerful tool in efforts to increase attendance at Pap smear screening.

2.2.4.2 Initial invitations and reminders

Many studies, in settings with only opportunistic screening, investigated the effect of an initial mailed invitation to Pap smear screening (Bowman et al., 1995; Pritchard et al., 1995; Torres-Mejia et al., 2000) and found that these increased compliance to screening. Since these results are not applicable in our setting, with an already established call-recall system, initial mailings will not be discussed further.

Only a few studies have focused on investigating eventual effects of different kinds of reminders on compliance at Pap smear screening. One reason could be that most research has been conducted in settings with opportunistic screening only. However, a subsequent reminder letter has been found to increase attendance (Berrino et al., 1979; Torres-Mejia et al., 2000), as did a phone reminder in a study about attendance at mammography (Taplin et al., 2000), and in a study on the combination of a physician's reminder letter and a phone contact (Lantz et al., 1995).

It is sometimes hard to disentangle what the investigators mean by reminders. For example, several of the “reminders” included in one meta-analysis of the effects of a patient reminder letter (Tseng et al., 2001) are merely reminders to the women that they are due for a Pap smear and are thus not comparable to a subsequent reminder following an initial invitation. In the mentioned meta-analysis, the non-subsequent reminders (or initial invitations) increased attendance at Pap smear screening (Tseng et al., 2001).

2.2.4.3 On-site screening

A positive effect has also been obtained in studies among minority groups by offering on-site screening when visiting a clinic or a hospital (Ansell et al., 1994; Mandelblatt et al., 1993:b; Margolis et al., 1998; White et al., 1993). This, one could say, may be an effective intervention to increase the efficiency of opportunistic screening (although it also introduces a risk for over-screening).

3 AIMS

The overall objective of our studies was to increase the understanding of the factors affecting compliance in Pap smear screening in a country with a population-based screening program, and to evaluate various measures taken to increase compliance to postal questionnaires and Pap smear screening. The specific aims were:

- To test how several practically relevant modifications of a questionnaire study (preliminary notification, length of the questionnaire, mention of a possible telephone contact) affect the response rate, and to investigate whether the response rate affected the partial non-response (Paper I).
- To identify predictors of non-attendance at Pap-smear screening, focusing on numerous background factors (such as socioeconomic status, gynecological history, risk behavior), knowledge (Paper II), and attitudes and beliefs (Paper III).
- To validate the reliability of self-reported screening (Paper II), and to test whether attitudes and beliefs differ if self-reported screening is used rather than true attendance status (Paper III).
- To test whether modifications of the invitation and call-recall system (added information, reminder letter, phone reminder) can increase compliance at Pap smear screening and to test whether more cytologic abnormalities thereby could be detected (Paper IV).

4 MATERIAL AND METHODS

Two types of epidemiological study designs were used in these studies; namely, the randomized controlled design (Paper I and IV) and the case-control design (Paper II and III). All studies were conducted in Sweden, a country that has exceptional opportunities for epidemiologic studies due to the ability to link individual information from different population-based registers through the national registration number. The national registration number is an individually unique identifier assigned to each inhabitant in Sweden at birth or immigration.

4.1 DATA SOURCES

In these studies we used one or more of the following of Sweden's population-based registers:

4.1.1 The National Population Register

Held by Statistics Sweden, this is the basic register of the population, continuously updated with information on current residents of Sweden. The most important information in the National Population Register is name, national registration number and residential address.

4.1.2 The Cytology Register in Uppsala County

Administrated by the Cytology laboratory at the University Hospital in Uppsala. All Pap smears taken in Uppsala County (both in organized and opportunistic screening) have been compiled in this register since 1969. The register is population-based and continuously updated concerning vital status, migration and deregistration (women who have personally asked to be excluded from the call-recall system, less than 0.01%). The register withholds information on women's name, national registration number, current address, invitations to and participation at screening, place of Pap smear test, diagnoses and treatments.

4.1.3 LOUISE Register

Held by Statistics Sweden, the LOUISE register is a longitudinal database on education, income and occupation during 1990-1999. Information on national registration number, demographic, educational and income variables, occupation and family composition is included.

4.1.4 The Swedish Cancer Register

Since the initiation of this nationwide registry in 1958, cancers have been coded according to the seventh edition of the International Classification of Diseases (ICD-7). All new cases are continuously registered in six regional cancer registers covering the whole country. On the basis of these registers the Cancer register is updated yearly. Nearly 100% of all diagnosed cancers are recorded and 98% of these are histologically verified. The proportion of registered cytologically or histologically verified cervical cancers was 100% in 2000. The Cancer Register includes information about name, national registration number, sex and domicile at the time of diagnosis, date of

diagnosis and the clinical and morphological diagnoses (National Board of Health and Welfare 2000).

4.2 PAPER I

4.2.1 Study design and subjects

We conducted a randomized controlled trial to evaluate various measures taken to increase the response rate to postal questionnaires. We also investigated whether these measures affected the partial non-response, i.e., missing answers in returned questionnaires. All men and women aged 20-79 years of age living in Sweden in May 1995 were identified through the National Population Register and constituted the source population for this study. From the register we drew a stratified random sample in two age groups, 20-49 and 50-79 years, with 1,000 subjects from each strata.

The questionnaire we used was part of the preparation for a case-control study about risk factors for kidney cancer (Bergström et al., 2001). The questionnaire consisted of questions about weight, diet, medical history and medication, physical activity, eating and drinking habits, tobacco use and certain background factors such as education and year and country of birth. Women were also asked about their reproductive history and men about their age at voice change. The alleged purpose given in the accompanying letter was to study risk factors for kidney cancer.

All participants received a questionnaire, a letter which explained the study and a prepaid return envelope. One reminder was mailed to all 2,000 subjects in the sample one week after mailing the questionnaire. Besides age and gender, each subject was characterized by population size at residence as well as by the weekday when the questionnaire was received (Tuesday or Friday). The questionnaires were sent in the beginning of July 1995. Subjects who had not answered within 75 days of the initial mailing were considered non-responders.

4.2.2 Interventions and randomization

Three factors were varied according to a randomized 2^3 factorial design. The *first* factor tested was sending or not sending a preliminary notification which preceded the mailing of the questionnaire by about 1 week and in which the study was presented and the questionnaire announced. The *second* factor tested was the length of the questionnaire. A long version included detailed questions about physical activity and food consumption (15 pages and 66 items for men and 18 pages and 79 items for women). A short version had less complex and shorter questions about physical activity and excluded all questions about food consumption (11 pages and 50 items for men and 14 pages and 66 items for women). The *third* factor tested was the inclusion or exclusion of a clause that mentioned the possibility of a future telephone contact requesting supplementary information if the questionnaire was incompletely answered. Those who received a questionnaire in which the telephone contact was mentioned were asked to provide their telephone number at the end of the questionnaire.

The three factors produced $2^3 = 8$ experimental conditions (treatments). Two-hundred-and-fifty subjects were randomly allocated to each condition, resulting in 1,000 subjects allocated to each factor modification.

The analysis of partial non-response was concentrated on questions that were common to all questionnaire types (31 questions for women and 28 for men).

4.2.3 Statistical methods

In the analyses of the overall questionnaire response rate we used logistic regression. The model was estimated by the maximum likelihood method; odds ratios (ORs) with 95 percent confidence intervals (CIs) were computed from the estimated parameters and standard errors. Univariate and multivariate models were estimated. Not only models with main effects but also those with interaction effects were estimated. Likelihood ratio tests were used to test different nested models against each other. On the basis of univariate analyses, confidence intervals for the difference between proportions are also shown in certain cases. These intervals were computed using a normal approximation.

In the modeling of partial non-response we used standard linear regression models estimated by ordinary least squares. The dependent variable was the proportion of questions not answered for each respondent.

4.3 PAPER II-III

4.3.1 Definition of non-attenders

To identify predictors of non-attendance at Pap smear screening, we conducted a case-control study among women living in Uppsala County. A non-attender (case) was defined in two different ways, depending on age: women aged 30-59 years who had *not* had a Pap smear within the last 5 years were defined as non-attenders, as were women aged 25-29 years who had *not* had a Pap smear within the last 3 years. The five-year interval was chosen since we wanted to investigate women who were truly non-compliant at Pap smear screening. The stricter definition was chosen for younger women, since a longer time interval would mean exclusion of this age group.

4.3.2 Study design and subjects

The participants in our study were sampled from a population comprising all (around 65,000) women aged 25–60 years resident in Uppsala County in December 1996. The study base was defined as all women who still resided in Uppsala County in December 1997. By linking the Cytology Register to the National Population Register we generated a database with individual information on *all* screening for cervical cancer in Uppsala County from 1969 through 1998, which included women with no registered smear as well. Screening information was supplemented until July 1, 1998, for all women included in the study. To be eligible for our study, a woman had to be alive on February 1998 and not have had a history of *in situ* or invasive cervical cancer.

From the study cohort we drew a random sample of 875 non-attenders and 750 attenders stratified into five-year age classes. Using information from the Cytology Register, all women in the study were categorized by the number of prior Pap smears taken, age when the last Pap smear was taken, the number of years since the last smear, and the type of screening (organized or opportunistic). Furthermore, population-size at the place of residence was retained for all interviewed women.

4.3.3 Data collection

All women were sent an invitation to participate in the study by means of a notification letter informing them about the purpose of the study. Then, between March 30 and June 19, 1998, telephone interviews were conducted by 19 professional female interviewers at Statistics Sweden. The study questionnaire was developed in a three-step procedure; (a) collecting questionnaires used in other similar studies, (b) unstructured personal face-to-face interviews to identify reasons for non-compliance, (c) a pilot questionnaire in a sample of 40 women to test the questionnaire. The final version of the questionnaire included 108 main questions and 56 sequential questions.

4.3.3.1 Paper II

In Paper II we concentrated on the following areas as predictors of compliance to screening: (1) socioeconomic and demographic factors; (2) genital symptoms and contraceptive use; (3) gynecological examinations; (4) risk behavior; (5) perceived health status and participation in other health-related activities; (6) knowledge and received information about the Pap smear and cervical cancer. We also validated the women's self-report on the Pap smear by comparing the women's answers to whether they had ever had a Pap smear, how often they had had a Pap smear, and when they had had their last Pap smear, with information from the the Uppsala Cytology Register.

4.3.3.2 Paper III

Paper III focused on the following potential predictors of compliance to screening: (1) social support and experience of cancer; (2) attitudes and beliefs concerning Pap smear screening, cervical cancer and treatment; (3) anxiety or worry about cancer or the Pap smear; (4) trust in the health care system; (5) reasons for non-attendance and future intentions regarding Pap smear screening; (6) preferences about information and screening. Questions about barriers to Pap smears screening were asked for both organized and opportunistic screening, and since no important difference between the two were found, the mean score of these questions was used for women who answered both. Several of the questions about attitudes and beliefs were constructed in line with the Health Belief Model (HBM) (Rosenstock, 1974; Rosenstock, 1990). Social support was assessed by means of three questions adapted from a social support instrument measuring the extent of social integration and attachment (Orth-Gomer et al., 1993).

Most of the questions about attitudes and beliefs were formulated as statements on a 6-point Likert scale (Kerlinger, 1986) ranging from 1 (completely disagree) to 6 (completely agree). Thirty-eight of these different items were retained in 17 final single- or multi-item subscales. These subscales were based on a factor analysis of *all* of the questions about attitudes and beliefs, and the reciprocal homogeneity within each subscale was tested with Cronbach's alpha (Cronbach, 1951) ranging from 0 to 1, where 0.6 or more was considered to be a sufficient value of internal consistency. The six multi-item subscales are described in Table 1. Each subscale contains the mean of a woman's answer to the questions included in that subscale. If more than one third of the answers were missing, the woman was treated as missing on that particular

subscale. Allowed missing answers were replaced with the mean of each woman's answers to the remaining questions on that subscale. The subscales were categorized into: agree, neutral and disagree. Questions not included in any subscale are presented in Table 2.

Table 1. Questions included in the subscales and homogeneity tests for each subscale.

Subscales	Items included
Satisfactory benefits Cronbach's $\alpha = 0.67$	Regular Pap smears gives feeling of control ^a Valuable to have a Pap smear regularly ^a Satisfied after a Pap smear ^a
Emotional barriers Cronbach's $\alpha = 0.86$	Does not like to have a Pap smear ^a Painful to have a Pap smear ^a Bothered by the thought of having a Pap smear ^a Examination unpleasant/embarrassing ^a Situation unpleasant/embarrassing ^a Health care in general unpleasant ^a Does not like to visit a gynecologist ^a
Time-consuming barriers Cronbach's $\alpha = 0.70$	Difficult to take time off from work ^a Priority of other more important things ^a Difficult to find off-duty time ^a Difficult to get to the venue ^a
Economical barriers Cronbach's $\alpha = 0.62$	Other problems, does not have the strength ^a Unnecessary if <i>no</i> symptoms ^a Unnecessary to go only for a Pap smear ^a The written invitation irritates ^a Too expensive ^a
Anxiety Cronbach's $\alpha = 0.66$	Afraid that something wrong will be detected ^a Thinking about getting cervical cancer (Yes/No) Uneasy talking about cancer ^a Uneasy when others talk about cancer ^a Affected if having a precursor lesion ^b
Social support Cronbach's $\alpha = 0.89$	Have someone to share interests with ^a Have someone to be familiar with ^a Have someone to consult for everyday concerns ^a

^a 6-point Likert scale: 1=completely disagree, 6=completely agree

^b 4-point Likert scale: 1=very affected, 2=fairly affected, 3=not especially affected, 4=not at all affected

Table 2. Questions not included in the subscales.

Components	Questions
Susceptibility	Believe I can have a precursor lesion (abnormality) Perceived risk of having cervical cancer
Severity	Severity compared to other cancer forms Chance to be cured if precursor lesion Chance to be cured if cervical cancer Treatment is worth while putting up with Cancer cannot be cured even if detected early
Benefits	Simple to have a Pap smear A negative Pap smear assures me I do not have cervical cancer Pap smear detects abnormalities before symptoms Pap smear reduces the risk for later treatment Pap smear reduces mortality due to cervical cancer
Barriers	I would be embarrassed if disease was detected I have had a negative experience of a visit to organized screening I have had a negative experience of a visit to a gynecologist I have heard of other that have had a negative experience Difficult to find a gynecologist that suits me Individual reasons for non-attendance in the past*
Cues to action	Been advised to have a Pap smear (By whom?) Been advised to <i>not</i> have a Pap smear (By whom?)
Anxiety/worry	Worried about the test results
Faith	Faith in the health care system
Future intentions	Likelihood of having a Pap smear in the future ^a Individual reasons for not wanting to attend in the future*

^a Likelihood of either responding to next invitation to organized Pap smear screening, or having a Pap smear at a gynecologist within one year.

* Open-ended question

4.3.4 Statistical methods

4.3.4.1 Paper II

Age-adjusted logistic regression was used to estimate ORs of being a non-attender over an attender, with 95% CIs. All variables that were statistically significant in the age-adjusted analyses (except hysterectomy) were thereafter employed to find the best-fitting multivariate model. To test different multivariate models against each other we used the likelihood ratio tests. We also used conditional logistic regression to estimate the ORs, which yielded only marginal differences (data not shown). To check for multicollinearity among the independent variables we calculated correlation coefficients between all independent variables included in the multivariate analysis. To elucidate how the socioeconomic variable profession was related to other explanatory variables, we fitted a separate multivariate logistic regression model with profession as a dichotomized outcome variable.

4.3.4.2 Paper III

Odds ratios and 95% CIs were used to estimate the relative risk of being a non-attender to screening for cervical cancer in an age-adjusted conditional logistic regression model. All variables that were statistically significant in the age-adjusted analyses were employed to find the best-fitting multivariate model. Likelihood ratio tests were used to validate different models against each other. In the multivariate analysis, the subscales were treated as *continuous* variables, standardized to the number of items in the subscales. Uncorrelated independent variables that were not included in the subscales were tested separately in the multivariate analysis.

In a separate analysis, the best-fitting multivariate model was controlled for the demographic and socio-economic variables included in Paper II: population size at place of residence (metropolitan areas, cities/towns, semi-rural/rural areas), education (9 years or less, 10-14 years, 15 years or more) and profession (white collar, blue collar, other). We tested for interactions among all of the explanatory variables in the multivariate model, assuming multiplicative interaction effects. To test the best-fitting multivariate model we conducted a Hosmer-Lemeshow goodness of fit test (Hosmer et al., 1989).

To investigate whether women's attitudes and beliefs were affected by the time since their last smear, we stratified the age-adjusted analyses on the time since the last smear for the non-attenders. All attenders acted as controls in these analyses. We also conducted separate multivariate analyses with attendance status based on women's self-reports only, that is, on the women's own perception about when they had had their last Pap smear.

4.4 PAPER IV

4.4.1 Study design and subjects

We conducted a randomized controlled trial to test whether modifications of the invitation and call-recall system can increase the compliance at Pap smear screening. Participants in our study were all women (12,240) invited to screening for cervical cancer in Uppsala County during 17 weeks during the spring of 2001. These eligible women were aged 25-59, lived in Uppsala County, had not had a Pap smear during the previous 3 years and had not asked to be excluded from the call-recall system.

All Pap smears taken after the invitation were recorded until March 15, 2002. Besides experimental condition and participation, each woman was categorized according to age, the time since the last smear and whether she had had a prior smear. Our database, with individual screening information, was linked to the LOUISE database at Statistics Sweden. This linkage enabled us to add individual information about the women's level of demographic and socioeconomic factors based on information from 31 December 1999.

4.4.2 Interventions and randomization

Three successive interventions to increase attendance at screening for cervical cancer were tested; namely, 1) modified invitation versus the standard invitation letter, 2) reminder letter to women who did not attend after the first intervention versus no

reminder letter, and 3) phone reminder to women who did not attend after the reminder letter versus no phone reminder.

1) The modified invitation letter consisted of sending an additional information brochure with the standard invitation. The brochure, entitled “A small examination of great importance”, was designed in collaboration with professionals at the Swedish Cancer Society and included additional information about the Pap smear, for example that the Pap smear is a preventive measure and why it is important to have a Pap smear when invited, as well as illustrative pictures and drawings of the female body showing the location of the cervix.

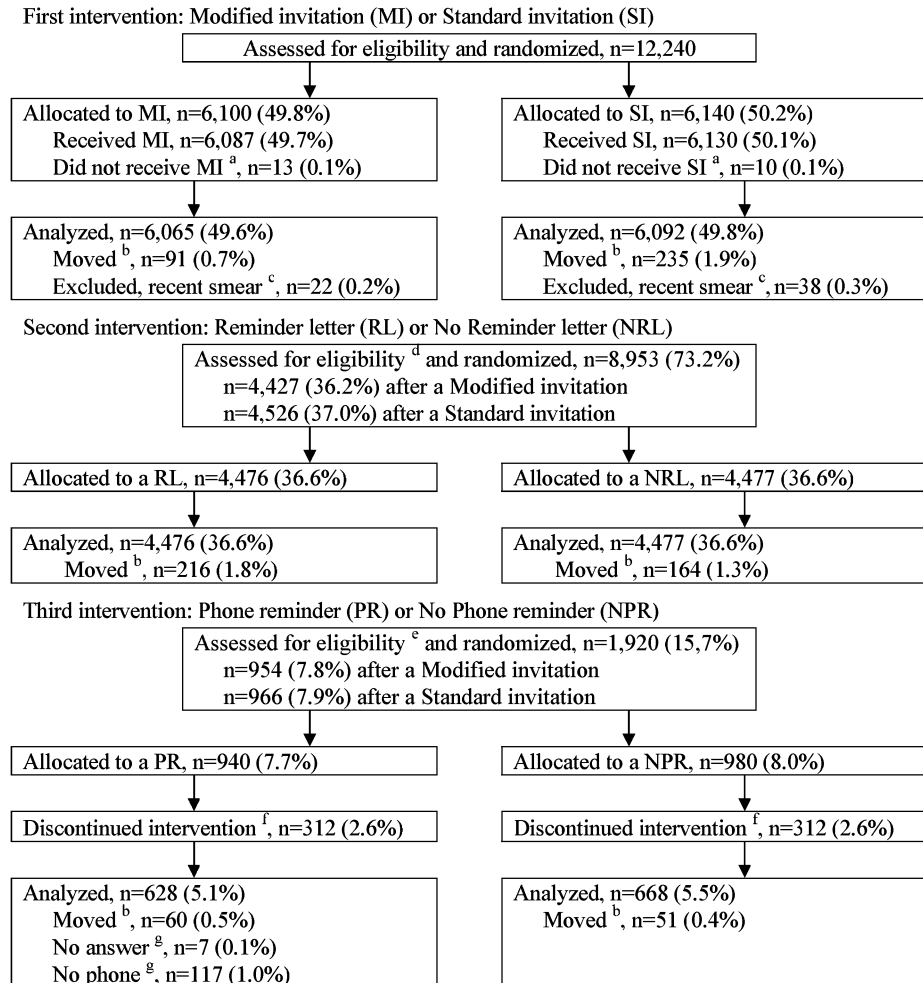
2) The reminder letter was identical to the standard invitation letter except that it included the information that the woman had received a prior invitation and that this was a reminder. The word “REMINDER” was printed in capitals in the heading.

3) Women who received a phone reminder were called up by one of two professional female research assistants who gave a short description of the Pap smear and offered women to schedule an appointment.

4) Women who did not receive any intervention, i.e., only received the standard invitation to organized screening, no reminder letter and no phone reminder composed the comparison group for the respective intervention groups.

Figure 3 summarizes the randomization process of the initial sample of 12,240 women on the three successive interventions. In the first intervention, all women were randomized every week to receive a modified or a standard invitation letter. All women who had not attended within 5 months after the first intervention were randomized to the second intervention, i.e., to receive a reminder letter or not. Women who remained non-compliant 2 months after the reminder letter were randomized to the third intervention, i.e. to receive a phone reminder or not. Only women receiving their first invitation during the first eight weeks of the study and who lived within Uppsala municipality were eligible to receive a phone reminder. Since the interventions were sequential, the endpoint of follow-up after the first and the second intervention was the starting point for the next intervention. The final endpoint of follow-up after the third intervention was one month after the last phone reminder was conducted.

Figure 3. Randomization of the participants in three successive interventions



In parantheses: Percent of the initial sample of 12,240 women

^a Deceased women and women who had requested to be excluded from the call-recall system (mainly due to hysterectomy), were excluded after the randomization and from further interventions.

^b We did not exclude women who had moved from the analysis due to differences in the postal tracking system between modified and usual invitations and since we did not have the corresponding information for women who did not receive any reminder.

^c Women who were invited to screening despite a recorded smear less than three years before the first intervention (mainly due to a time lag between taking a smear and getting it registered in the cytology register), were excluded after the randomization.

^d Women who had not attended within 5 months after the first intervention were eligible for the second intervention.

^e Women who had not attended within 2 months after the reminder letter and who were randomized to the first intervention in one of the 8 first weeks during spring 2001 were eligible for the third intervention.

^f Women living outside Uppsala municipality did not receive a phone reminder.

^g We did not exclude women who were not reached by phone from the analysis since we did not have corresponding information for women who did not receive any phone reminder.

4.4.3 Statistical methods

The analyses were performed according to the intention-to-treat principle. The results of the interventions were analyzed using a generalized linear regression model with identity link, assuming that the probability of participation after an invitation was binomially distributed. The results are expressed as absolute differences, with 95% CIs between the proportion of women participating in the intervention group and the control group. We also compared the results from a univariate logistic regression model with those from a multivariate logistic regression model, adjusting for screening history and demographic and socioeconomic factors. The model assumes that the logarithm of the odds of attending is a linear function of the explanatory variables; ORs with 95% CIs were computed from the estimated parameters and standard errors. Occurrence of mediating effects of the background factors on the interventions was checked by testing for homogeneity over the categories for these background factors in the generalized linear additive model described above.

The fraction attending screening within 12 months in the different intervention groups was estimated from the proportions attending at the times of the different types of interventions. We had information on attendance after 12 months for 9,560 women, thus including only these in the analysis. The confidence intervals given are based on the estimated standard errors obtained by error propagation using Gauss' approximation after a logarithmic transformation of the product of probabilities constituting the twelve-month participation rates. Corresponding analyses of the proportions of cytologic abnormalities (CIN1+ and CIN2+) were also performed. Furthermore, the formal statistical tests of differences in proportions of cytologic abnormalities between the different interventions were compared by means of Fisher's exact test. Due to the small number of events, the type of initial invitation (i.e., standard or modified) was disregarded in these analyses. Since only women living in Uppsala municipality were included in the phone reminder intervention, we compared cumulative effects of these women with all women in the country, but found attendance only marginally higher.

We separately analyzed the effects of screening history and demographic and socioeconomic variables on attendance, regardless of intervention, again using a logistic regression model. The main outcome measure was the proportion of women attending screening within six months after the first invitation.

5 RESULTS

5.1 PAPER I

We received completed questionnaires from 975 of the 2,000 selected subjects, corresponding to an overall response rate of 49%. The sample consisted of 49% women and 51% men.

5.1.1 Demographic characteristics

Independently of experimental conditions, we analyzed the proportion of respondents according to age, sex, population size and weekday of mailing. Age influenced the response rate markedly. Less than 40% of the subjects under the age of 35 returned their questionnaires. For the 40- to 74-year age group, the response rate varied between 47 and 57%, that is, up to 20% higher than in the youngest age group. In the oldest age group (75-79 years), the response rate was again slightly lower (44%). A model with age in continuous form including a second-order term confirmed the non-linear relation. Overall, the response rate among women was 8% higher than among men (53% compared to 45%) and the response rate was 7% higher in rural areas than in metropolitan areas (52% compared to 45%). The only variable that did not significantly affect the response rate was the weekday of mailing, where the response rate among those who received the questionnaire on a Tuesday was 4% higher than for those who received it on a Friday (51% compared to 47%).

5.1.2 Interventions

5.1.2.1 Preliminary notification

Of the three randomized factors, preliminary notification had the greatest impact on the response rate (Table 3). This increased the response rate by 7% (95% CI 3 to 11), from 45% with no preliminary notification, to 52%. We also analyzed the effect of the design variables in different strata of the background variables to see whether there was any effect modification. Non-significant, but quite large differences were found for age, where people older than 40 years seemed to be more sensitive to preliminary notification, and for the weekday of mailing, where preliminary notification appeared to be more useful when the questionnaire reached its addressee on Friday.

5.1.2.2 Length of the questionnaire

A short questionnaire increased the response rate by 5% (95% CI 0 to 9), from 46% with the long questionnaire, to 51% (Table 3). The effect was of borderline significance. One statistically significant effect modification, albeit barely significant at the 5% level, was with regard to sex. Men seemed to be particularly attracted by a short questionnaire.

5.1.2.3 Possible telephone contact

Mention of the possibility of a telephone contact entailed a non-significant 4% (95% CI -1 to 8) lower response rate (Table 3).

Table 3. Odds ratios (ORs) and 95% confidence intervals (CIs) of receiving a completed questionnaire with experimental modifications in three factors, Sweden 1995

	Sample size	Respondents		Univariate modeling		Multivariate modeling ^a	
	(no.)	No.	%	OR	95% CI	OR	95% CI
Preliminary notification							
Yes	1,000	522	52.2	1.32	1.11-1.57	1.30	1.08-1.56
No	1,000	453	45.3	1.00	(ref.)	1.00	(ref.)
Short questionnaire							
Yes	1,000	511	51.1	1.21	1.01-1.44	1.24	1.04-1.48
No	1,000	464	46.4	1.00	(ref.)	1.00	(ref.)
Telephone							
Yes	1,000	469	46.9	1.00	(ref.)	1.00	(ref.)
No	1,000	506	50.6	1.16	0.97-1.38	1.14	0.95-1.37

^a This model included the variables: allocation group of each factor, age categories in 10-year classes, sex, population size, and weekday of mailing.

As expected in a randomized trial of sufficient size, the results of the multivariate modeling (which included the additional variables age categorized in 10-year classes, sex, population size, and weekday of mailing) were similar to those of the univariate modeling (Table 3).

5.1.2.4 Combined effects

The highest response rate, with the three factors combined, was observed in category 4 (preliminary notification, short questionnaire, no mention of telephone contact), and the lowest in its opposite category 5 (no preliminary notification, long questionnaire, mention of telephone contact). The response rate in category 4 was 16% higher than in category 5 (95% CI 7 to 24), 56% vs. 40% (that is, almost a 40% increase). A test for interaction between the three random assignments was not significant (using a likelihood ratio test we obtained $\chi^2(3) = 4.17$, $p > 0.05$). Hence, we can largely rely on the main-effects model. Factorial design categories 1 (preliminary notification, long questionnaire, mention of telephone contact) and 8 (no preliminary notification, short questionnaire, no mention of telephone contact) gave higher response rates than would be expected on the basis of the main-effects model (52% and 53%, respectively).

5.1.3 Partial non-response

The effects of the design modifications on partial non-response were moderate. Preliminary notification was associated with a slightly higher and statistically non-significant mean proportion (0.9%) of missing answers compared to no preliminary notification. The longer questionnaire entailed no significantly higher proportion of missing answers than did the short questionnaire, nor did mention of a telephone contact seriously affect the partial non-response. When the effects were combined, category 5, which showed the lowest questionnaire response rate, had the lowest proportion of missing answers. Although the differences between the means were, on the whole, not large (up to 2%, corresponding to a 59% increase in the proportion of missing answers), multivariate analyses showed that categories 1 and 4 had a

significantly greater number of missing answers relative to category 5. We related the questionnaire response rates to the mean proportions of missing answers for the eight observation points constituted by the various experimental conditions and found a strong positive correlation (Pearson correlation coefficient = 0.82, $p = 0.01$). Thus, the gains from a higher questionnaire response rate were to some extent counteracted by a higher mean proportion of missing answers. However, since the gains in questionnaire response were much larger than the losses due to partial non-response, the net effects of the studied factors on total response – that is, the total number of answered questions that we received from the 2,000 subjects – were essentially the same as the effects on questionnaire response.

The greatest differences in partial non-response were found between the various age groups. The mean percentage of missing answers in the oldest group, 70-79 year olds, was more than 5% higher than in the group, aged 30-49, who showed the lowest proportion of missing answers. No differences in partial non-response were found between men and women. Also, those who answered only after a reminder letter had a minimally but significantly (1%) higher partial non-response than the others. This effect disappeared after adjustment for age, since older people were overrepresented among those who required a reminder to answer.

5.2 PAPER II-III

Of the sampled 1,625 subjects, 1,334 (82%) could be reached by phone and 1,018 (76%) of them completed the interview. Of the interviewed 504 non-attenders, 74 (15%) were ineligible and subsequently excluded because they had either had a Pap smear between the notification letter and the interview or stated that they had had a recent Pap smear outside Uppsala County. This left us with 944 subjects, corresponding to a response rate of 430 non-attenders (69%) and 514 attenders (81%) of the women who were reached and eligible.

The Cytology Register allowed us to compare women who agreed to telephone interviews and those who did not. We found a higher proportion of non-attenders that had had their last Pap smear within 6-9 years ago among those who agreed to telephone interviews than those who did not (51% vs. 40%, $p=0.002$). Furthermore, a lower proportion of non-attenders that had never had a Pap smear was observed among those who agreed to telephone interviews than those who did not (10% vs. 23%, $p<0.001$). Also, the mean number of prior smears differed somewhat between non-attenders who agreed to telephone interviews and those who did not (4.2 respectively 3.7 prior smears, $p=0.03$). No differences in screening history were found among attenders who agreed or did not agree to be interviewed. However, there was a higher proportion of attenders aged 42-51 years among those who agreed to telephone interviews than among attenders who did not (33% vs. 24%, $p=0.01$).

5.2.1 Validity of self-reports (Paper II)

In order to validate how accurately women recalled their screening history, we compared the interview answers with information from our database. To the question “Have you ever had a Pap smear”, 99% of the attenders and 95% of the non-attenders gave a correct answer. However, among women without a single smear registered in

the database, 50% (21 out of 42) believed that they had had one. The women's recall of the year when they had their last smear was less accurate. Among attenders, 74% gave the correct year, whereas among non-attenders only 29% did ($p<0.001$). Only 14% of the attenders underestimated the time that had elapsed since the last Pap smear compared to 57% of the non-attenders ($p<0.001$) (50% stated that they had had a smear within five years and 29% within three years). In fact, as many as 53% of the non-attenders would have been incorrectly classified as attenders had the study defined attendance status on the women's self-report instead of the database, whereas only 5% of the attenders would have been incorrectly classified as non-attenders. The results were largely the same whether the women had attended organized or opportunistic screening. Irrespective of attendance status, the longer the time since the last smear, the smaller the proportion of women who gave a correct answer.

5.2.2 Demographic and socioeconomic factors (Paper II-III)

In the age-adjusted analysis, population size, employment status and profession significantly affected attendance status, whereas education, marital status and number of children did not. Non-attenders were more likely to be living in semirural or rural areas than in metropolitan areas; in fact, non-attendance increased with a decreasing density of population ($p=0.001$). Also, non-attenders were more likely to be currently non-employed and blue-collar workers.

Only population size retained its effect after controlling for other variables in the multivariate analysis (Table 4-5). Although profession no longer contributed significantly to the model when other explanatory variables were entered, it was related to several of them (population size, contraceptive use, frequency of condom use, smoking, on whose initiative the smear was taken, frequency of visits to a physician). This was revealed in a multivariate analysis when profession was used as the outcome.

5.2.3 Risk behavior and gynecological history (Paper II)

Several factors relating to risk behavior, contraceptive use and gynecological history affected attendance in the age-adjusted analysis. Women who had had no intercourse or had had only one sexual partner during the last five years were more likely to be non-attenders than were women with two or more sexual partners. Non-attenders were also more likely than attenders to always use a condom during sexual intercourse and to smoke; indeed, the higher the number of pack years, the greater the risk of non-attendance ($p=0.008$). Also, non-attenders were more likely to use other contraceptives than oral or not to use any contraceptive method at all and to have had a hysterectomy, and were less likely to have had menstrual disturbances or genital problems. Age at first intercourse and at menopause did not affect attendance status.

Non-attendance was also more common among women who had *not* seen a gynecologist on a regular basis than among those who had (OR=4.4, 95% CI 3.2-5.9). The most common reason why a non-attender had not visited a gynecologist during the last 4 years was that they either felt healthy (39%) or that they had no other reason for a visit, such as prescriptions for oral contraceptives (32%). Also, women who had seen different gynecologists or only one once, or who gave symptoms or pregnancy as their most usual reason for seeing a gynecologist, were more likely to be non-attenders than were women who had always seen the same gynecologist or who gave health check-

ups as their most usual reason. Women who had explicitly asked for Pap smears when seeing a gynecologist were more likely to be attenders than were women who only had had smears on the gynecologist's initiative. However, 60% of the non-attenders stated that they had been to a gynecologist during the last 3 years, and 37% of them believed they had had a Pap smear during the same time.

Whereas the number of sexual partners did not retain its effect in the multivariate analysis, frequency of condom use did, i.e., the probability of non-attendance was higher among women who always used a condom during intercourse (Table 4). There was also a tendency that non-attenders were more likely to be smokers than were attenders, although the estimates were no longer statistically significant in the multivariate model. Contraceptive use, on whose initiative the smear was taken, and whether the woman visited the same gynecologist or not remained strong predictors of non-attendance in the multivariate analysis. Compared with women who used oral contraceptives, those who used condoms or no contraceptives at all were three to seven times more likely to be non-attenders than others. Women who were used to seeing different gynecologists were also more likely to be non-attenders, as were women who had *not* had Pap smears on their own initiative and who had *not* had genital problems.

5.2.4 Health behavior and health status (Paper II)

Attendance status was not affected by the woman's perception of her own health status but by participation in other health-related activities in the age-adjusted analysis. There was a tendency, although not statistically significant, that women who had not participated in mammography were more likely to be non-attenders. Future intentions towards mammography had a stronger effect, that is, more non-attenders than attenders stated that they did not intend to participate in mammography. Women who never saw a physician and those who saw one more than five times per year were both more likely to be non-attenders than were those who saw one 1-5 times per year. The frequency of visits to a physician remained a strong predictor of non-attendance in the multivariate analysis, i.e., women who visited a physician more than five times a year or never were more likely to be non-attenders (Table 4). Non-attenders were also more likely than attenders to feel dubious towards future mammography.

5.2.5 Information and knowledge (Paper II)

Whereas information about the Pap smear and female cancer did not affect attendance status in the age-adjusted analysis, several differences in knowledge were found. Non-attenders were more likely than attenders to *not* know the *main* purpose of the Pap smear (to detect precursor lesions to cervical cancer), to *not* know of the recommended screening interval (every third year) or believe it was less often, and to *not* know what treatments are available for precursors to cervical cancer. We found no significant differences between non-attenders and attenders in knowledge about the recommended age at the *first* or *last* smear, which type of cancer the Pap smear is aimed to prevent, or which are the risk factors for cervical cancer. When controlling for other variables, only knowledge about the recommended screening interval retained its effect (Table 4). Women who thought that the recommended screening interval was longer than three years were more than twice as likely to be non-attenders than were women who knew the recommended interval.

Table 4. Best-fitting multivariate model of the probability of being a non-attender expressed as odds ratios (ORs) and 95% confidence intervals (CIs). All estimates are controlled for age at interview.

	Multivariate modeling ^a	
	OR	95% CI
Population size		
Metropolitan areas	1.00	(ref.)
Cities or Towns	1.40	0.95-2.06
Semi-rural or Rural areas	1.54	1.07-2.21
Genital symptoms, last 5 years		
No	1.00	(ref.)
Yes	0.56	0.38-0.85
Contraceptive use, last 5 years		
Oral contraceptives	1.00	(ref.)
Depo-Provera, Norplant, IUD, Diaphragm	2.69	1.56-4.64
Condom, spermicides etc.	3.40	1.83-6.31
None	6.85	3.70-12.68
Visit same/different gynecologist		
Same	1.00	(ref.)
Different	1.90	1.34-2.70
Only once	1.46	0.82-2.60
Never been to a gynecologist	2.35	1.23-4.48
Initiative to smear at a gynecologist		
Only on gynecologist's initiative	1.00	(ref.)
On own initiative	0.43	0.29-0.62
Never had a smear at a gynecologist	1.10	0.73-1.68
Use of condoms, last 5 years		
Always	1.88	1.02-3.47
Sometimes	1.22	0.75-2.00
Never	1.00	(ref.)
Likelihood of future mammography		
Very likely	1.00	(ref.)
Fairly likely	2.00	1.19-3.38
Not likely	1.35	0.52-3.54
Frequency of visits to a physician, last 5 years		
>5 times/year	3.12	1.45-6.70
1-5 times/year	1.00	(ref.)
Less than once/year	1.09	0.77-1.52
Never	1.78	1.09-2.90
Recommended screening interval		
Every 3 rd year	1.00	(ref.)
More often	1.07	0.75-1.52
Less often	2.16	1.20-3.89
Do not know	2.76	0.84-8.99

^a This analysis was based on 479 attenders and 373 non-attenders. Missing answers was mainly due to the question about initiative to smear (12 attenders and 46 non-attenders).

Independently of attendance status, many women (34%) believed that the *main* purpose of Pap smears was to detect cancer and, as a corollary, the most frequent answer to the question of how precursors were treated was radiation (34%). Only 40% of the women believed that they would have a very big chance to be cured if a precursor to cervical cancer was detected. There also seemed to be a frequent misunderstanding about which type of cancer the Pap smear is intended to prevent, since the most common answer was “cancer of the uterus” (45%). Some women (29%) also believed that the Pap smear protects against more than one cancer type. The most common answers to the questions about how often and during how long a time women are recommended to have Pap smears were “every 2nd year” and “all their lives” (39% and 43%, respectively). To a multiple choice question about risk factors, the most common answer for both non-attenders and attenders was hereditary causes (40%), and the second most common answer were “I do not know” (28%), whereas multiple male partners came in fourth place (15%), sexually transmitted diseases in fifth place (9%), smoking in seventh place (8%) and young age at the first sexual intercourse in ninth place (2%). Only 111 non-attenders (26%) and 152 attenders (30%) gave at least one correct answer.

5.2.6 Attitudes and beliefs (Paper III)

5.2.6.1 Susceptibility, severity and anxiety

Whereas non-attendance was negatively associated with a perceived risk of having a precursor lesion (abnormality), no association was found for a perceived risk of having cervical cancer in the age-adjusted analysis. On the other hand, non-attenders did *not* perceive cervical cancer to be as severe as other cancer forms, whereas attenders did. However, no significant difference was found for women’s beliefs in the chance to be cured if they had cervical cancer. Non-attendance was negatively associated with perceiving treatment to be worthwhile, even if the chance of being cured was small, and with experienced anxiety about cancer and the Pap smear. In the multivariate analysis, only severity and anxiety retained its effect (Table 5). Non-attendance was negatively associated with perceived severity compared to other cancer forms and with anxiety. We found an interaction between anxiety and initiative to take a Pap smear ($p<0.05$), and with the perceived risk of having a precursor lesion ($p<0.05$). Women with high levels of anxiety were more likely to take the initiative to a Pap smear upon visiting a gynecologist and also perceived themselves to be at greater risk.

5.2.6.2 Benefits and barriers

In the age-adjusted analysis, non-attendance was negatively associated with the satisfactory benefits of having a Pap smear, the belief that it is simple to have a Pap smear and with faith in the accuracy of the Pap smear, as well as a general faith in the health care system. No significant difference was found between non-attenders and attenders in perceiving the Pap smear to be efficient in detecting abnormalities before symptoms or in reducing the risk of later treatment. Non-attendance was positively associated with emotional, time-consuming and economical barriers toward having a Pap smear, whereas there were no differences between non-attenders and attenders in perceived embarrassment if a disease was detected during examination. Non-attenders were not more likely to have had a past negative experience of a gynecological examination. On the contrary, attenders were more likely to report that they had been

dissatisfied with a prior visit to a gynecologist (OR=0.7, 96% CI 0.5-1.0). In the multivariate analysis, non-attendance was still negatively associated with satisfactory benefits, but positively associated with time-consuming and economical barriers (Table 5). The other benefits and barriers no longer showed significant effects on attendance status when we controlled for potential confounding variables. We found one significant interaction amongst the variables included in the multivariate model; namely, between time-consuming barriers and anxiety ($p<0.05$). Women with high levels of anxiety were less likely to report time-consuming barriers.

Table 5. Multivariate odds ratios (OR) and 95% confidence intervals (CI) of non-attendance to cervical cancer screening for variables in the best fitting model.

	Multivariate analyses ^a		Multivariate analyses ^b	
	OR	CI	OR	CI
Severity compared to other cancer forms ^c				
Worse	1.0	(ref.)	1.0	(ref.)
Alike or less severe	1.9	1.1-3.4	1.8	1.0-3.3
Satisfactory benefits (subscale)	0.7	0.6-0.8	0.7	0.6-0.8
Time-consuming barriers (subscale)	1.2	1.1-1.5	1.3	1.1-1.5
Economical barriers (subscale)	1.7	1.2-2.5	1.7	1.2-2.5
Anxiety (subscale)	0.9	0.8-1.0	0.9	0.8-1.0

^a Estimated OR adjusted for age. The model only includes women with complete data on all variables (391 non-attenders and 472 attenders). Missing answers were mainly due to the economical barrier index (22 attenders and 11 non-attenders) and benefits index (10 attenders and 15 non-attenders). The Hosmer-Lemeshow goodness of fit statistic equaled 3.48 ($df=8$, $p=0.90$), indicating a good model fit.

^b Estimated OR adjusted for age and demographic and socio-economic variables population size (metropolitan areas, cities/towns, semi-rural/rural areas), education (<9 years, 10-14 years, 15-) and profession (white-collar, blue-collar, other). The model includes only women with complete data on all variables (388 non-attenders and 467 attenders).

^c Categorized variable

5.2.6.2.1 Barriers in relation to the time since the last smear

When we stratified the non-attenders according the time since their last Pap smear, we found that the longer the time-lapse since the last smear, the greater the differences in barriers between non-attenders and attenders. The odds ratios for emotional barriers were 0.6, 1.2 and 1.3 for non-attenders who had not had a smear in 3-5 years, 5-10 years or 10 years or more, respectively. The corresponding odds ratios for time-consuming barriers were 1.0, 1.4 and 1.5, and for economical barriers 1.3, 2.4 and 3.9.

5.2.6.3 Cue to action, social support and experience of cancer (Paper III)

We found no differences between non-attenders and attenders in the likelihood of being advised to have a Pap smear or of having a relative or a friend with a precursor lesion or cancer in the genital tract. Non-attenders were, however, more likely to have received the advice to have a Pap smear by a family member or a friend than to have received it by a gynecologist or a physician (OR=4.9, 95% CI 2.3-10.8). The stated degree of social support was negatively associated with non-attendance in the age-

adjusted analysis, but not in the multivariate analysis. We found an interaction between social support and economical barriers ($p < 0.001$). Women with low levels of social support were more likely to express economical barriers.

5.2.6.4 Attitudes in relation to self-reported attendance status (Paper III)

When we based attendance status on self-reported screening instead of information from the database, the best-fitting model was somewhat altered (Table 6). All of the results in the multivariate model, except for time-consuming barriers, showed a tendency of being strengthened. Self-reported non-attendance was also positively associated with perceived emotional barriers. Clear differences also existed in attitudes and beliefs between non-attenders who self-reported as non-attenders and attenders. The former group behaved in about the same way as did *all* self-reported non-attenders, whereas the only significant difference between non-attenders who self-reported as attenders and true attenders were that the former group did not perceive Pap smear screening as beneficial. There were no great differences in either age distribution or screening history between the two groups of non-attenders, which could explain these differences.

5.2.7 Preferences and future intentions (Paper III)

5.2.7.1 Preferences

Although significantly more non-attenders than attenders preferred to have the test taken by a midwife or at a certain location (14% difference), significantly more attenders preferred to have the test taken by a gynecologist or a general practitioner (20% difference). Independent of attendance status, most women preferred to receive an invitation when they are due for a Pap smear (86%), and a prearranged time in that invitation (60%). However, more non-attenders than attenders stated that they would *not* have a Pap smear if they could not have it at the preferred location (8% vs. 5%), without an invitation (52% and 22%, respectively) or a pre-arranged time (25% vs. 6%). No differences were found between non-attenders and attenders in preference for the gender of the smear taker. Overall, most women did not think that the gender of the smear-taker mattered (51%), or preferred a women (47%), whereas only a few women preferred a man (2%). Non-attenders and attenders also differed in how they preferred to receive information about the Pap smear. Although significantly more non-attenders than attenders preferred to receive information in writing (9% difference), significantly more attenders preferred it face-to-face (10% difference).

5.2.7.2 Future intentions

Three-hundred and ten non-attenders (72%) and 462 attenders (90%) stated that they would very likely either respond to the next invitation to organized screening or to have a Pap smear at a gynecologist within one year ($OR = 3.5$, 95% CI 2.4-5.0). The most common reasons why non-attenders would not attend after an invitation were that they thought it unnecessary because they felt healthy, had reached menopause or did not need a prescription for oral contraceptives (26%); lack of time or temporary impediments (18%); anxiety about the test or the examination (15%). Intent to have a Pap smear was associated with age: older women were less likely than younger women to intend to participate in future screening.

Table 6. Multivariate odds ratios (ORs) and 95% confidence intervals (CIs) of non-attendance to cervical cancer screening for variables in the best fitting model when attendance status were based on self-reported screening.

	Self-reported attenders vs self- reported non- attenders ^a		Attenders vs non- attenders who self-reported as non-attenders ^b		Attenders vs non- attenders who self-reported as attenders ^c	
	OR	CI	OR	CI	OR	CI
Severity compared to other cancer forms						
Worse	1.0	(ref.)	1.0	(ref.)		
Alike or less severe	2.5	1.1-5.4	4.7	1.7-13.3		
Satisfactory benefits (subscale)	0.7	0.5-0.8	0.6	0.5-0.8	0.8	0.7-0.9
A negative Pap smear assures me I do not have cervical cancer						
Agree					1.0	(ref.)
Neutral					1.5	1.0-2.3
Do not agree					1.7	0.9-3.4
Emotional barriers (subscale)	1.3	1.1-1.5	1.2	1.0-1.4		
Time-consuming barriers (subscale)	1.3	1.0-1.5	1.4	1.1-1.8		
Economical barriers (subscale)	2.1	1.4-3.2	2.4	1.5-3.9		
Anxiety (subscale)	0.8	0.7-1.0	0.8	0.7-1.0		
Social support (subscale)	-	-	0.8	0.7-1.0		

^a Estimated OR adjusted for age. The model only includes women with complete data on all variables (199 self-reported non-attenders and 656 self-reported attenders).

^b Estimated OR adjusted for age. The model only includes women with complete data on all variables (179 non-attenders self-reporting as non-attenders and 471 true attenders).

^c Estimated OR adjusted for age. The model only includes women with complete data on all variables (220 non-attenders self-reporting as attenders and 501 true attenders).

Table 7. Proportion of women participating in screening within 6 months after the first invitation by demographic and background factors.

	Sample size (No.)	Participated within 6 months No.	%		Sample size (No.)	Participated within 6 months No.	%
All women	12,157	3,593	29.6				
Age				Citizenship			
24-29 years	2,941	771	26.2	Swedish (born Swedish)	10,322	3,124	30.3
30-39 years	3,542	1,084	30.6	Swedish (born Other)	1,000	277	27.7
40-49 years	2,895	922	31.9	Other (born Swedish)	44	7	15.9
50-59 years	2,779	816	29.4	Other (born Other)	784	181	23.1
Years since last smear				Marital status			
3-4	5,475	2,512	45.9	Married/Cohabitants	6,430	2,116	32.9
5-32	3,654	475	13.0	Single, own home	5,230	1,379	26.4
0 smear, 24-26 years	1,535	413	26.9	Living with parents	491	94	19.1
0 smear, 27-59 years	1,493	194	13.0	Have children			
Country of birth				Yes	6,284	2,030	32.3
Sweden	10,370	3,134	30.2	No	5,867	1,559	26.6
Other Nordic country	492	145	29.5	Education			
Other EC country	111	33	29.7	Low	1,950	494	25.3
Poland	52	8	15.4	Intermediate	5,185	1,630	31.4
Former Yugoslavia	87	21	24.1	High	4,842	1,447	29.9
Other European country	107	21	19.6	Employment status			
USA and Canada	41	8	19.5	Employed/Student	9,344	2,898	31.0
South/Central America	109	28	25.7	Seeking employment	1,001	303	30.3
Africa	128	23	18.0	Early retirement	980	242	24.7
Turkey	66	19	28.8	Unemployed/housewife	826	146	17.7
Iran	169	40	23.7	Disposable income ^b			
Middle East	189	48	25.4	0-50% of median	812	163	20.1
Asia	198	57	28.8	50-100% of median	5,272	1,554	29.5
Former Soviet Union	30	7	23.3	100-200% of median	5,447	1,684	30.9
Oceania	7	1	14.3	200-% of median	620	188	30.3
No. of years in Sweden ^a				Social welfare			
1-5	190	42	22.1	Yes	929	207	22.3
6-10	383	91	23.8	No	11,228	3,386	30.2
11-20	532	131	24.6				
21-	650	187	28.8				

* When the numbers do not add up to the 12,157 women studied, it is due to missing observations (from 1 to 180) in the LOUISE database (based on information from 31 December 1999).

^a Including only women who were born outside Sweden.

^b The median disposable income=99,300 SEK.

5.3 PAPER IV

The analysis on the first intervention was based on 6,065 (49.7%) women who received a modified invitation and 6,092 (50.1%) who received a standard invitation letter. In the second intervention, the analyses were based on 4,476 (36.6%) women who received a reminder letter and 4,477 (36.6%) women who did not. In the third intervention the analysis was based on 628 (5.1%) women who did receive a phone reminder and 668 (5.5%) women who did not.

5.3.1 Baseline characteristics

Reflecting our large sample size, the baseline characteristics were evenly distributed within each intervention group. During the process of three subsequent randomizations there was a gradual increase in the proportion of women who were younger, more higher educated, single, nulliparous and immigrants. Furthermore, except for women with higher education, these women were over-represented among women not reached by the phone reminders, as were women with no prior Pap smear and on social welfare.

Independently of experimental conditions, we analyzed the proportion of attenders according to screening history and demographic and socioeconomic variables. All background variables significantly affected attendance six months after invitation in a univariate analysis. The greatest difference was related to screening history. Women with the greatest need for Pap smear screening due to a long time lapse since the last smear or having never had a smear, also had the lowest attendance rates (Table 7). The youngest women, invited to screening for the first time, also had a low attendance rate.

The country of birth affected attendance, with the lowest attendance rates among women born in Oceania, Poland, Africa, USA and Canada and Eastern Europe (Table 7). Number of years living in Sweden and of citizenship also affected attendance, i.e., the longer the women had lived in Sweden the greater was the attendance, as was attendance if the women had Swedish citizenship. The country of birth also interacted with a number of demographic and socioeconomic variables, such as parity, income and social welfare. There was a tendency that women born in Sweden, but with one or both parents born in a Middle Eastern country had a lower participation rate. The group was, however, too small for meaningful analysis. Marital status, parity, education, employment, income and social welfare also affected attendance, with a lower attendance rate among women who were single, nulliparous, had a low education, not employed/student, were poor or on social welfare.

5.3.2 Interventions

5.3.2.1 *Modified invitation*

We found no measurable effect of the modified invitation compared to the standard invitation (Table 8). The modified invitation resulted in a 1% (95 CI -3 to 3) higher response rate after five months, from 26% with the standard invitation to 27%. Only women aged 30-44 years were more likely to attend after a modified invitation than after a standard invitation, which gave an increase of 3% (95% CI 1 to 6), from 26% after a standard invitation to 29%. We also analyzed the effect of the design variables in different strata of the background variables to see whether there was any effect modification. Only one significant effect modification, albeit barely significant at the

5% level, was with regard to age. Women aged 30-44 years were more likely to attend after a modified invitation than the youngest women ($p<0.05$).

5.3.2.2 *Reminder letter*

A reminder letter increased the proportion attending by 9% (95% CI 8 to 11), from 6% with no reminder letter to 16% (Table 8). Having had a prior smear, education, social welfare and marital status significantly modified the effect of the second intervention. Women who had had a prior smear were more sensitive to a reminder letter than were those who had not had a prior smear ($p<0.001$), as were women with intermediate education ($p<0.05$), women who were not on social welfare ($p<0.01$), and women who were married/cohabitant ($p<0.001$).

5.3.2.3 *Phone reminder*

Of the three randomized interventions, the phone reminder had the greatest impact on the attendance rate (Table 8). This increased the attendance rate by 31% (95% CI 27 to 36), from 10.0% with no phone reminder to 41%. Age, having had a prior smear, social welfare and having children significantly modified the effect of the third intervention. Women aged 30 years or older were more sensitive to a phone reminder than were the youngest women ($p<0.01$), as were women who had had a prior smear ($p<0.001$), women who were not on social welfare ($p<0.05$), and women who had children ($p<0.05$). Of the 628 women randomized to receive a phone reminder, 444 (71%) were actually reached and, of those, a total of 250 (56%) women attended. Of the 194 women who were reached but did not attend, 66 (34%) had scheduled for a Pap smear but did not show up, and 128 (66%) declined, chiefly because they had a temporary impediment, preferred a private midwife or gynecologist or experienced fear or anxiety.

Table 8. Odds ratios (Ors) and 95% confidence intervals (CIs) of participating in screening after randomized intervention.

	Sample size (no.)	Participated in screening		Univariate modeling		Multivariate modeling ^a	
		No.	%	OR	95% CI	OR	95% CI
First intervention							
Modified invitation	6,065	1,638	27.0	1.1	1.0-1.2	1.0	0.9-1.1
Usual invitation	6,092	1,566	25.7	1.0	(ref.)	1.0	(ref.)
Second intervention^b							
Written reminder	4,476	693	15.5	2.7	2.4-3.2	2.9	2.5-3.3
No written reminder	4,477	282	6.3	1.0	(ref.)	1.0	(ref.)
Third intervention^b							
Phone reminder	628	260	41.4	6.3	4.7-8.5	6.9	5.0-9.4
No phone reminder	668	67	10.0	1.0	(ref.)	1.0	(ref.)

^a Controlling for experimental condition, and for all background factors included in Table 1-2.

^b Since no wash-out period existed between the interventions a displacement in attendance might be expected.

As expected in a randomized trial of sufficient size, the results of the multivariate modeling were similar to those of the univariate modeling. The multivariate analyses, which adjusted for potential confounders, changed our effect measure only marginally.

5.3.3 Cumulative effects

The cumulative effects of different combinations of sequential interventions on attendance and on the number of detected cytologic abnormalities were estimated 12 months after the first randomization (Figure 4).

5.3.3.1 Interventions

The attendance rate after 12 months for a standard invitation letter only was 33% (95% CI 33 to 34) and for a modified invitation only, 36% (95% CI 35 to 38). The modified invitation thus shows a long-term effect of around 3% (Figure 4). However, there was no evidence of a significant difference caused by the modified invitation for women who received the phone reminders.

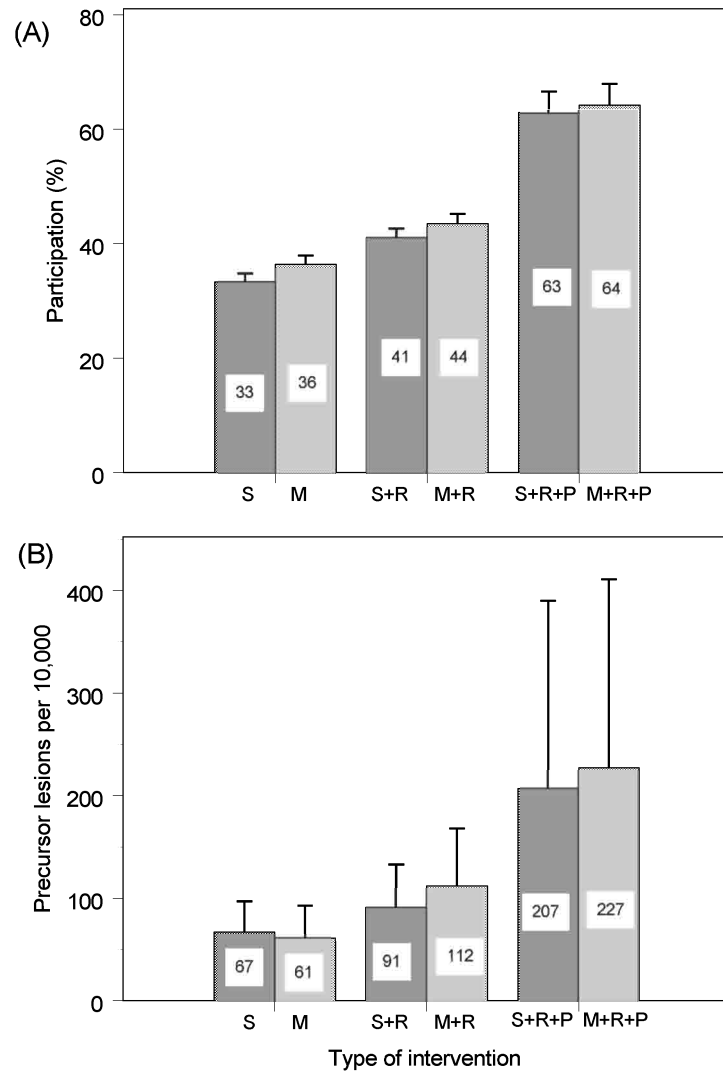
The combination of modified invitations and reminder letters gave a cumulative attendance of 44% (95% CI 42 to 45), that is, an 11% higher attendance rate compared to that observed with a standard invitation letter only.

By combining modified invitations, reminder letters and telephone reminders, a cumulative attendance of 64% (95% CI 61 to 68) was reached, that is, the attendance rate was almost doubled compared to that observed with a standard invitation letter only.

5.3.3.2 Diagnosis

The cumulative number of women diagnosed with CIN1+ was tripled by using the combination modified invitation, reminder letter and phone reminder (227 per 10,000 women), compared to the standard invitation only (67 per 10,000 women) (Figure 4), corresponding to a 239% (95% CI 103 to 464) increase in the number of detected cytologic abnormalities. Both women who received a reminder letter only and a reminder letter in combination with a phone reminder yielded significantly higher numbers of CIN1+ diagnoses compared to those receiving the initial invitation only ($p<0.0012$ and $p<0.0001$, respectively). Corresponding differences were also demonstrated for the number of CIN2+ diagnoses ($p=0.03$ and $p=0.004$, respectively).

Figure 4. Proportion of women participating in Pap smear screening (Panel A), and rate of precursor lesions (CIN1+) (Panel B), within 12 months from first randomization, by selected combinations of interventions and reference point (no intervention).



S=Standard invitation (reference), M=Modified invitation, S+R=Standard invitation+Reminder letter, M+R=Modified invitation+Reminder letter, S+R+P=Standard invitation+Reminder letter+Phone reminder, M+R+P=Modified invitation+Reminder letter+Phone reminder.

6 GENERAL DISCUSSION

6.1 METHODOLOGICAL CONSIDERATIONS

6.1.1 Study design

The choice of study design depends on the nature of the dependent variable under investigation, type of exposure, feasibility, ethical considerations, and the available resources. Two of the studies in this thesis were based on a case-control design (Paper II-III) and two were based on experimental designs (Paper I and IV).

The participants in our case-control study (Paper II-III) were sampled from a cohort of all women living in Uppsala County for which individual information on screening history was available. We needed a case-control design since it provided an opportunity to evaluate the risk of being a non-attender to screening in relation to a wide range of exposures, collected through telephone interviews. Another reason why we chose the case-control design was cost-effectiveness and time.

The participants in our first randomized controlled intervention were sampled from the population-based national population register and included a random sample of 2000 men and women aged 20-79 years (Paper I). The participants in our second randomized controlled intervention were sampled from a population-based register consisting of information on all women due for screening in Uppsala County (Paper IV). A randomized controlled intervention is a type of prospective cohort study where the exposure status of each participant is randomly assigned by the investigator. The participants in our studies were identified on the basis of their exposure status and were followed to determine whether they would respond to the questionnaires or attend Pap smear screening. Intervention studies are considered to provide the most reliable evidence from epidemiologic studies due to the randomization of participants to an exposure, which means that both known and unknown confounders are controlled for.

The accuracy of the studies in this thesis – as with any epidemiological study – depends on the absence of error in estimation. Such errors can be either random or systematic. Precision corresponds to lack of random error and validity to lack of systematic error (Rothman et al., 1998).

6.1.2 Precision

Random errors are the variability in data that cannot be explained. Precision can be increased through increased study sample size and by increasing the efficiency with which information is obtained from a given number of study subjects. To evaluate the role of chance in epidemiologic research always involves the performance of a test of statistical significance; the most informative measure produced being the confidence interval. We used 95% confidence intervals to provide information about the precision of our studies. A statistically significant result does not mean that chance cannot have accounted for these findings, only that such an explanation is unlikely. The large number of participants in our intervention studies yielded high statistical power for most analyses, which is reflected by fairly narrow confidence intervals (Paper I and IV). Greater variability in the estimates existed for some of the more unusual exposures

in the case-control study (Paper II-III), which can imply that the sample size was inadequate to exclude chance as an explanation for the findings in these cases. To increase the efficiency in the case-control study (Paper II-III) we also matched cases and controls by age-strata. However, since several exposure-outcome associations were examined simultaneously in this study, we cannot ignore the potential role of chance in producing particular results.

Another important determinant of precision is the extent of exposure misclassification, in the form that the instrument used actually measures what it is supposed to. This can be evaluated by comparing the degree of conformity between two measures with the same instrument. The results presented in Paper II and III are very similar to a parallel study about non-attendance to mammography screening in which the questionnaire was almost identical (Lagerlund et al., 2000:b; Lagerlund et al., 2000:a).

6.1.3 Validity

Validity is the degree to which a measurement is free from bias (systematic error). The validity is usually separated into two components, namely internal and external validity (or generalizability). Systematic errors that detract from internal validity are often classified into three broad categories; namely, selection bias, information bias and confounding.

6.1.3.1 Selection bias

Selection bias is error due to systematic differences in exposure status of the selected study subjects and those who theoretically should be eligible for the study (including non-participants). Selection bias is especially a problem in case-control studies.

The population-based design of our case-control study reassured us that the selection of cases and controls were not related to their exposures (Paper II-III). However, the non-response could introduce a selection bias if women who chose to participate in the study differed from those who did not. In our case-control study the response rate of 69% among non-attenders was relatively low compared to 81% among attenders, showing that non-attenders were also more likely to be non-respondents. This problem, which is common in studies on screening behavior (Kant et al., 1994), is hard to overcome. Furthermore, the comparison of respondents and non-respondents showed under-representation of never screened women among the responding non-attenders. However, the likely net effect of this is that we underestimated the magnitude of any differences between non-attenders and attenders. One should keep in mind, though, that this could mislead us in trying to evaluate which factors are important.

Selection bias should not be a problem in our intervention studies (Paper I and IV), since the samples were population-based and because of the randomized design. Since all selected subjects contributed information, whether they responded or not, selection bias due to drop-outs after randomization was not a problem in these studies.

6.1.3.2 *Information bias (observation bias)*

Information bias can arise if the information is obtained, reported or interpreted differently among groups in the study.

6.1.3.2.1 Misclassification of attendance status

The major strength of our case-control study (Papers II-III) is the population-based design and access to a database covering *all* cytological screening in the area during the last 30 years. This should eliminate the misclassification that arises when attendance status is based on organized screening only (Elkind et al., 1988), or on self-reports (Paskett et al., 1996; Suarez et al., 1995; Walter et al., 1988:b). Such misclassification of attendance status would attenuate any true association. Some women defined as non-attenders may, however, have had a Pap smear outside of Uppsala County. A total of 40 non-attenders reported that they had had a Pap smear in another county during the defined period. All of these women were excluded from the analysis, although this probably meant that we excluded true non-attenders, since many women underestimated the time elapsed since the last smear. Of course, there is a small risk that a few non-attenders had forgotten that they had had a Pap smear outside of Uppsala County. This would lead to an underestimation of the results.

One possible flaw in the case-control study (Papers II-III) is the less stringent criteria used to define non-attendance among the youngest women (25-29 years). This group was too small for meaningful stratified analyses of all possible predictors of non-attendance. However, the differences between non-attenders and attenders tended to be smaller in this age group.

In our intervention studies (Papers I and IV), the analyses were performed according to the intention-to-treat principle and we did not exclude participants who had moved or were not reached. Some participants had moved when the studies were conducted, although the continuously updated population registers in Sweden ensured that this group was not large. Since all participants, independently of the intervention group, had had the same possibility to move, this would be non-differential among participants who were randomized for intervention or not, which would cause a slight underestimation of the effects that would not greatly affect our conclusions. In the second intervention study (Paper IV), a somewhat larger proportion of women could not be reached by the phone reminders, mainly due to not having a listed phone number. This is also non-differential with respect to intervention and would lead to underestimation of any differences. Women who were not reached for a phone reminder were mainly younger, most probably students who sometimes do not have a listed phone number, women who were born outside Sweden, or foreign visitors (or women who had not yet received Swedish citizenship). However, one potential weakness in this study (Paper IV), was that there was a difference in time between receiving the first invitation and the reminder letter depending on the week of randomization. This should, however, not have any bearing on the results, since the women were matched by week of randomization and time at attendance was not a variable of interest.

6.1.3.2.2 Misclassification of exposure

In case-control studies where information is gathered by interviewers, there is always a risk that the interviewers affect the answers from the participants, especially if they are aware of the case-control status (interviewer bias). This would lead to a differential misclassification that would overestimate the differences. In our case-control study (Papers II-III) the professional interviewers were unaware of the case-control status and did not know our definition of cases and controls. The participants answered questions about attendance at both organized and opportunistic Pap smear screening as well as questions about other gynecological examinations. It would therefore be difficult for the interviewer to disentangle the true case-control status. If the interviewers were able to figure out attendance status it would have been based on self-reported attendance. Any influence of the interviewers on the answers given by self-reported attenders and non-attenders, would lead to an exaggeration of the differences between these groups.

Another potential problem is the retrospective design of the case-control study (Paper II-III), which means that the women answered questions about past behavior. If cases and controls report events in a non-comparable manner, we would have a recall bias. Compliance to screening can itself affect attitudes and beliefs about Pap smear screening. To achieve consonance (Festinger, 1957), a person may support or motivate the decision taken. Hence, there is a risk that reasons given for non-attendance may be post hoc justifications rather than actual reasons (King, 1987). Also, women who had no prior opinion about Pap smear screening may have felt forced to take a stand when they were asked the questions. If this tendency differs between non-attenders and attenders it might lead to a biased result. However, these problems should not be of great importance in our study, since only 10% of the non-attenders had never had a Pap smear, and as many as 53% of the non-attenders self-reported as attenders.

This type of exposure misclassification can be evaluated by comparing the degree of conformity between two measures with two different instruments. In general, the results presented in Papers II and III are in line with several previous studies on compliance at Pap smear screening (King, 1987; Lantz et al., 1997; Orbell et al., 1995; Peters et al., 1989).

There was no risk of misclassification of exposure in the intervention studies, since the participants were randomly allocated to the exposures by the investigators (Papers I and IV). None of the collaborator in the studies had any possibility to affect who received the exposure and only the professional assistants conducting the phone reminders in the second intervention study (Paper IV) were aware of exposure status beforehand. Furthermore, none of the participants in the intervention studies were aware that the allocated exposures were part of an investigation.

6.1.3.3 *Confounding*

Confounding is a bias resulting from an unbalanced distribution of other causes among people in different exposure categories. A confounder has to be related to exposure and, independently of that exposure, be a risk factor for the disease.

In Sweden, true causes of attendance at Pap smear screening are not known. Assuming that some of the factors that have been proven to affect compliance to screening in

studies performed in other countries also apply to Swedish women, we collected information on many potential predictors in the case-control study (Papers II-III). All variables that were statistically significant in the age-adjusted analyses (except hysterectomy) were thereafter employed to find the best-fitting multivariate model.

The major strength of our randomized controlled trials (Paper I and IV) was the randomized study design, conducted with large samples. This enabled us to perform a valid analysis of the intervention effects and to look for mediating effects among subgroups of the study subjects. A randomized design is the only valid way to demonstrate the eventual effects of different interventions, since it allows for control of both known and unknown confounders. Due to the randomized design our findings are probably internally valid. In the first randomized trial (Paper I), the results of multivariate modeling were similar to those of the univariate modeling (Table 3), meaning that our findings were not confounded by age, gender, population size or weekday of mailing.

The second randomized trial (Paper IV) was conducted on a large sample of women who were due for a Pap smear during almost four months. The multivariate analysis indicated that our findings were not confounded by the demographic and socioeconomic variables age, having had a prior smear, education, employment status, disposable income, social welfare, marital status, having children, country of birth, or citizenship (Table 8). We had, however, a slightly higher estimate in the multivariate analysis of the third intervention (mainly due to age and social welfare), which lead to underestimation of the effect of a phone reminder in the crude analysis. This is probably a reflection of the fact that the women not living in Uppsala municipality were excluded after the random allocation to a phone reminder or not.

6.1.3.4 Generalizability (external validity)

Assuming that the roles of chance, bias and confounding have not seriously affected our results, we can assess the applicability of our findings to other populations. Provided that the internal validity is satisfactory, the population-based design used in all our studies should further give a high external validity,

In the first intervention study (Paper I), the participants were selected from the general population, which should at least make our results generalizable to all men and women in Sweden. Because our interventions were non-specific and the effects were fairly robust over the strata of background factors, we believe that our findings are generalizable to other settings. Many of our findings were also in accordance with studies performed in other settings and in other research areas.

The case-control study was conducted within one Swedish county (Paper II-III). Since women were randomly selected within the non-attender and attender groups it should be no problem to generalize these results to Uppsala County (taking into consideration the differential non-response between the two groups). Can our results be generalized to the rest of the country or even to settings outside Sweden? The mix of organized and opportunistic screening differs over the country, but we found no major impact of the type of screening on our results. Given that women do not differ geographically in their

behavior, we believe our results can be generalized to the whole country. They may also be important in other settings, given the objective definition of attendance and the coverage of all screening within a defined area. In fact, much of our results were in accordance with studies performed in other settings.

As in the case-control study, the second intervention study was conducted within Uppsala County (Paper IV). Since the intervention study was integrated with the ordinary call-recall system for cervical cancer screening we were able to include all women due for screening during a defined time period. Furthermore, since the cytology register is population-based, our results should be generalizable to all women born in Sweden in relevant ages due for Pap smear screening. Because our interventions were non-specific and the effects fairly robust over the strata of numerous background factors, we believe that our findings are indeed generalizable to other settings with high quality screening programs.

6.2 INTERPRETATIONS AND IMPLICATIONS OF FINDINGS

6.2.1 Increasing response rate to postal questionnaires (Paper I)

The overall questionnaire response rate in our first intervention study of 49% may seem low. Even in the “best” category, the response rate was only 56%. We have no information about the individual reasons for not returning the questionnaire. Our questionnaire was of average size and complexity for an epidemiological study. In the covering letter, the purpose of finding risk factors for kidney cancer was explained. Although the questionnaire was sent out during the summer, when a high proportion of the addressees may have been away from home, many have their mail forwarded to their summer address. It was probably more important that only one reminder was sent out and that no other follow-up measures were taken. In one study (Marrett et al., 1992), a response rate of about 50 percent with one reminder was increased to 70 percent by a second reminder. This is approximately the same response rate as in several case-control studies in the Swedish population (Bergkvist et al., 1988; Galanti et al., 1996). A second reminder would probably have increased the overall response rate, but it might also have changed the relative importance of each of the three design modifications. Repeated reminders have been found to lessen the effect of incentives and length (Kalantar et al., 1999; Marrett et al., 1992; Spry et al., 1989), whereas the effect of preliminary notification has been consistent even after repeated reminders (Spry et al., 1989).

6.2.1.1 Demographic characteristics

The demographic factors age, gender and population size were significant determinants of response propensity, but did not confound our findings. We, as others, received a lower response rate among subjects younger than 40 years (Parkes et al., 2000) and older than 74 years (Kelsey et al., 1989). The topic of the study and how it concerns the participant may partially explain the low response rate among the youngest age group. Our study explicitly dealt with risk factors for kidney cancer, and younger people may be less concerned about such diseases that typically occur in old age. A possible explanation for the lower response rate among the oldest includes a higher prevalence of physical or mental diseases and visual impairment in that age group, as well as a more suspicious attitude (Kelsey et al., 1989). The oldest age group (70-79 years) had also

a higher proportion of missing answers. This may be partly related to the type of questions that we asked. Many questions dealt with circumstances far back in time, requiring older people to tax their memories further back than younger people.

As in another study (Marrett et al., 1992), women in general and people living in rural areas had a higher response rate. The effect of gender on response rate may even be underestimated, since women received a somewhat longer questionnaire, whereas the effect of residential area may, in part, be explained by the different age structures between urban and rural areas. More research is needed to determine whether men and women evaluate health issues differently and whether they should be approached and motivated differently.

6.2.1.2 Interventions

6.2.1.2.1 Preliminary notification

Of the manipulations that we tried, the preliminary notification had the greatest impact on the response rate. This is well in line with results from sociologic and marketing research (Edwards et al., 2002; Fox et al., 1988; Harvey, 1987; Linsky, 1975; Spry et al., 1989; Yu et al., 1983). Reasons may be that people are forewarned of the questionnaire and interest for the investigation may be raised before the main mailing, when no direct action is required. The preliminary notification may further give an impression that the study is important as well as establishing the legitimacy of the study.

6.2.1.2.2 Length of the questionnaire

Whether and how the length of the questionnaire affects the response rate is a very important issue in most research areas, since more information might be obtained by using a longer questionnaire. We found a higher questionnaire response rate with the shorter version of the questionnaire, although of borderline significance. The results of previous studies are not consistent. One reason for this could be that the effect may require a large relative difference in the number of pages. Neither our data nor the available literature gives an unequivocal answer as to whether a linear dose-response relationship or a threshold effect exist between the length of the questionnaire and the response rate. Moreover, effects of the length are likely to be confounded by the content: the difference in response rate may be due to the presence or absence of particular questions rather than to the length. (This can be seen clearly in our study, where women who generally had a higher response rate than men, also received a longer questionnaire.)

Despite the weak and inconsistent empirical support, short questionnaires are often recommended in epidemiological studies because of concern about the willingness of people to respond. Our findings belie some of these concerns. It may be more rewarding to pay attention to details in mailing procedures and to increase people's motivation than to cut out pages in the questionnaire. One prior study has also shown that the benefits of the increased information obtained by a longer questionnaire outweigh a potential non-response bias due to a somewhat longer questionnaire (Lund et al., 1998).

6.2.1.2.3 Possible telephone contact

Mention of a telephone contact reduced the questionnaire response rate, but only marginally. Furthermore, it did not affect the partial non-response in the way one might have suspected. This, to our knowledge, is the first study to investigate the effects of such information that is commonly found in mailed questionnaires. It is conceivable that some perceived the phone contact as a greater encroachment on their privacy and were therefore less willing to participate. However, we did not observe a positive effect on partial non-response.

6.2.1.2.4 Combined effects

It has been suggested that combinations of many manipulative aspects, rather than one single technique, should be used to increase the response rate (Dillman, 1978). Our results support this hypothesis, as do other studies where other combinations were used (Kalantar et al., 1999; Pemeger et al., 1993; Spry et al., 1989). However, there exists substantial heterogeneity among the results of different studies (Edwards et al., 2002), which implies that it may be inappropriate to combine results to produce a single estimate of effect, unless they have been shown to have a mutual effect in a randomized trial.

6.2.1.3 *Partial non-response*

There was a clear positive relationship between questionnaire response rates and the mean proportions of missing answers. This suggests that the marginal addition of participants resulting from our efforts to increase the response rate was recruited from a less motivated stratum of the population. The moderate losses due to partial non-response did not outweigh the overall gains produced by the mailing modifications. Our findings, however, show a negative side of zealous attempts to increase the response rate at all costs. We were unable to analyze the validity of the answers in the various subgroups, but a high partial non-response rate may indicate a lower validity of the answers.

In conclusion, simple modifications of mailing strategies and of the questionnaire itself may strongly influence the subjects' willingness to respond. The best combination of modifications yielded a response rate that was almost 40 percent higher than the rate obtained with the worst combination. Preliminary notification substantially increased the questionnaire retrieval rate, but the length of the questionnaire had less effect. Demographic factors such as age, gender and population size were significant determinants of response propensity, but did not confound our findings. The effect of questionnaire length was, however, modified by gender.

6.2.2 Factors affecting attendance at Pap smear screening (Paper II-IV)

In our case-control study (Papers II-III), several predictors of non-attendance were identified and the reliability of self-reported screening was validated. In the intervention study (Paper IV), additional possibilities to explore the effects of screening history, and demographic and socioeconomic variables appeared.

6.2.2.1 Validity of self-reports (Paper II-III)

We, as others (Paskett et al., 1996; Suarez et al., 1995; Walter et al., 1988:b), found that women tend to underestimate the time lapse since their last smear. Misclassification of attendance status would attenuate any true association and would introduce bias of unpredictable direction if the perception of attendance were associated with important determinants of attendance. Indeed, in one study almost all predictors of screening became insignificant when medical charts rather than self-reports were used to truly distinguish non-attenders from attenders (Paskett et al., 1996). In our study the perception of attendance was associated with several important determinants of attendance. As a conclusion, self-reports on screening should be treated with caution.

In our study, over half of the non-attenders self-reported as attenders and 30% reported as having had a Pap smear within the recommended screening interval. One reason could be that many women may not be able to distinguish between Pap smears and pelvic exams (Paskett et al., 1996), thus believing that a Pap smear was included in the gynecological examination that they had undergone. As a corollary, a non-attender more seldom than an attender takes her own initiatives to have a Pap smear.

6.2.2.2 Demographic and socioeconomic factors (Paper II-IV)

Our results confirm with others (Berrino et al., 1979; Hesselius et al., 1975) that the attendance is lower amongst the youngest participants (24-29 years), and especially so amongst those invited for the first time to Pap smear screening (24-26 years with no prior Pap smear) (Paper IV). We can offer no explanation as to why these women have a greater resistance to attend. The tendency that the differences between non-attenders and attenders were smaller in this age group (Papers II-III) may imply that the predictors of non-attendance that we investigated may not conform to this group. In one recent study, women aged 20-39 differed in many respects from women aged 40-59 (in likelihood to seek a doctor when experiencing symptoms, anxiety about the test and worry while waiting for the result) (Idestrom et al., 2002). Moreover, although the attendance was increased in this age group by additional efforts (Paper IV), the effect was not as high as in other age groups. Special research about reasons for non-attendance among the youngest women and motivations to increase attendance may be needed.

Our results (Paper IV) do not support the notion that women over the age of 50 have a lower participation rate (Bergmann et al., 1996; Berrino et al., 1979; Calnan, 1985; Mandelblatt et al., 1999; Maxwell et al., 2001; Nicoll et al., 1991; Orbell et al., 1996:a), although older women were more likely to state that they did not intend to participate in future screening (Paper III). Differences in attitudes toward use of and familiarity with health care, as well as structural differences in the health care system between different countries could be possible explanations for these contrasting results.

6.2.2.2.1 Residence and immigration

In agreement with other studies about compliance at Pap smear screening (Katz et al., 1994), the attendance rate was lower among women living in rural areas (Paper II). Longer distances to the maternity wards or less access to a gynecologist are possible reasons why these women may be more reluctant to participate at screening.

We also found that immigrant women (especially from non-Nordic and non-EC countries) had a lower attendance rate than women born in Sweden (Paper IV), as immigrant women in other settings as well (Hewitt et al., 2002; Maxwell et al., 2001). Although there were too few women to allow meaningful analysis of single ethnic groups, both the number of years of stay in Sweden and citizenship may partly explain these differences. Temporal residence in Sweden, language barriers and knowledge of the Swedish health care system, as well as eventual cultural differences in perception of preventive health care, could be possible explanations. Since the lower attendance rate was found among several women born in countries with a fairly high incidence of cervical cancer (such as eastern European countries and Africa), further attempts to explore predictors of non-attendance as well as to increase attendance in these groups are needed.

6.2.2.2.2 Marital status, parity and socioeconomic status

In contrast to our case-control study (Paper II), but in line with results from other studies (Hewitt et al., 2002; Katz et al., 1994; Maxwell et al., 2001; Segnan, 1997), we found a small effect of marital status, parity and education in the univariate analysis in our intervention study (Paper IV). One explanation for this discrepancy could be that we underestimated the effects of these variables in the case-control study due to a bias caused by non-response (non-respondents are overrepresented among subjects from lower socioeconomic groups (Richiardi et al., 2002)). However, although these variables showed effects in the univariate analysis (Paper IV), they were small. Probably the effect of these variables would even be of less, or no, importance if potential confounders could be controlled.

In the case-control study (Paper II), the effect of employment status and profession did not have an effect on attendance status in the multivariate analysis. In Sweden, traditional economical barriers to utilizing health care have been removed, and if socioeconomic status is related to economical barriers to utilizing health care, it may affect our results. However, studies in other settings, with other conditions, have reached similar results (Lantz et al., 1997; Peters et al., 1989). Moreover, in a comparison between a country with universal insurance coverage (Canada) and a country without it (USA), the attendance among poor women was similar (Katz et al., 1994), meaning that other predictors than out-of-pocket cost affect attendance in this group. In our study, women who were blue-collar workers were also more likely to live in rural areas, to not use oral contraceptives, to always use a condom during intercourse, to smoke and to not take the initiative to a Pap smear.

6.2.2.3 *Gynecological history (Paper II-III)*

In accordance with prior research (Peters et al., 1989), we found that most women have had Pap smears as part of a gynecological examination (Paper II). The non-attenders and attenders did, however, differ in their use of gynecological health care, mainly depending on the choice of contraceptive method. Whereas the attenders were more likely to use oral contraceptives (which entails regular visits), non-attenders were more likely to use a condom or to not use any contraceptives at all. The cause-effects of choice of contraceptive method and gynecological visits are unknown to us (whether the choice of contraceptive method depends on gynecological visits, or whether

gynecological visits depend on the choice of contraceptive method). But prior oral contraceptive use do increase the likelihood for Pap smears in the future, even after the women have stopped using oral contraceptives (Spurlock et al., 1992). To go for check-ups although one feels healthy is also commonly mentioned by attenders in relation to pregnancy, birth control and gynecological issues (Forss et al., 2001). Since the main reason among non-attenders for not visiting a gynecologist was that they had felt healthy (thus indicating that they do understand, or repress the fact that one can be ill without having any symptoms), they may not perceive gynecological visits in the same way. Moreover, women who do not feel the need to have gynecological examinations for any other reason may not conceive the Pap smear, in itself, as reason enough to visit a gynecologist or a midwife.

To visit the same gynecologist is also important. This may be the effect of a better doctor-patient relation, which has been found to be related to compliance through a greater satisfaction with medical care and a better understanding and recall of the information given (Ogden, 2000; Roter et al., 1996). It is probably also easier for gynecologists to keep track of the screening history of regular patients. However, since most women at some point in time undergoes a gynecological examination, whether it is with a certain gynecologist or midwife, or at a certain clinic or venue, opportunities do exist for communication and advice about Pap smear screening (which is a cue-to-action to attend). Advice from a doctor may also be taken more seriously than advice from family members and friends.

6.2.2.4 Health behavior and health status (Paper II)

Non-attenders were more likely both to have a low and high frequency of visits to a physician (Paper II). To have a high frequency of contacts with a physician could imply chronic disease or other medical problems, and possibly less concern about other health problems. To never see a physician is probably an indicator of good health, but can also imply repression of health problems, fear of the health care, a fatalistic view of disease, poor economy or lack of time.

The non-attenders were *not* as likely to take their own initiative to have a Pap smear or to intend to participate in future mammography and were more likely to smoke (Paper II). This may imply a difference between attenders and non-attenders in general health behavior, a concern about health problems and a belief that they can carry out a recommended action (self-efficacy).

6.2.2.5 Information and knowledge (Paper II-III)

More non-attenders than attenders believed that the Pap smear should be taken at longer intervals than recommended (Paper II), as was also found by others (Peters et al., 1989). This misconception would entail that even if a woman were positive to having a Pap smear, she might be examined too infrequently. No other differences in received information or knowledge were found, except for preferences in receiving information about the Pap smear (Paper III). Although attenders were more likely to prefer a situation where face-to-face information was possible (indicating a trust in the provider's ability to give advice and providing an opportunity for questions and direct action), non-attenders preferred information in writing.

Although most women reported that they had received information about the Pap smear, knowledge about these issues was poor among most women (Paper II). Whether this is because women read the information but do not understand it or remember it correctly, or that they do not read the information or confuse it with that about other cancer types is not known. In any case, our results are in agreement with others (Foxwell et al., 1993; Hesselius et al., 1975; Idestrom et al., 2002; Peters et al., 1989) stating that many women do not understand the true benefit of Pap smear screening, believe that the main purpose is to detect existing cancer, and do not know which cancer the Pap smear is targeted to prevent. Since the possibility of having a disease without knowing it in combination with understanding of the importance of early detection may be an important benefit (Forss et al., 2001), information about the nature of the Pap smear obviously needs to be improved. Women who do not understand the benefits may not participate due to anticipated anxiety and may see little value of having the test (Elkind et al., 1988; Foxwell et al., 1993; Peters et al., 1989).

General knowledge about risk factors for cervical cancer was, as in other studies (Fylan, 1998; Kowalski et al., 1994; Price et al., 1996), poor (Paper II). This implies that most women were not aware of the protective role of condom use, which was also found in another Swedish study, where only 13% were aware of the protective role of condom use (Idestrom et al., 2002). Another possibility is that most women cannot make a realistic appraisal of their own risk for cervical cancer.

Knowledge about the risk factors of HPV as a sexually transmitted agent might be a potential problem for compliance, since some women still seem to believe that sexually transmitted reflects character flaws (King, 1987), which they do not want to be associated with. In one study, few women with cervical abnormalities, although mentioning the association with sexual transmission, accepted sexual transmission as an explanation for their condition, and instead explained it by stress (Kavanagh et al., 1997). Further investigation is needed to evaluate whether the higher non-attendance amongst the youngest in our setting (Paper IV) is associated with a suggested better knowledge about risk factors for cervical cancer (Idestrom et al., 2002; King, 1987; Kowalski et al., 1994; Neilson et al., 1998).

6.2.2.6 Risk behavior, perceived susceptibility and anxiety (Paper II-IV)

Sexual risk behavior was *not* more common among non-attenders (Paper II). This result conforms to others (Ciatto et al., 1991; Orbell et al., 1995), where sexual risk behavior was instead positively associated with attendance. In fact, non-attenders in our study were more likely than attenders to protect themselves from contracting sexually transmitted diseases by always using condoms during intercourse. A protective behavior may, in itself, lead to less need to seek medical care. Non-attenders were also less likely to have had genital symptoms (which may be an important cue-to-action). A past experience of genital problems may mean a stronger feeling of vulnerability and a high acknowledgement of the importance of gynecological health care, something that might outweigh eventual barriers to attend. Non-attenders were, however, slightly more likely to smoke, which could indicate an increased risk for cervical cancer, and more importantly, the strongest predictor of non-compliance in the intervention study (Paper IV) was insufficient prior attendance. That is, women having the greatest cause to attend screening were more likely to be non-attenders.

We found no differences between attenders and non-attenders in perceived susceptibility to cervical cancer (Paper III), although it might have been difficult for many women to answer this question based on their knowledge.

More importantly, in contrast to prior studies (Kowalski et al., 1994; Murray et al., 1993;b; Orbell et al., 1995), the non-attenders did not feel as anxious about the test result and about cancer as did attenders. Non-attenders were also less likely to take the initiative to a Pap smear when visiting a gynecologist and were less likely to intend to participate in future screening (feel healthy, past menopause). Although no difference in susceptibility was found, this indicates that the women indirectly make some appraisal of their susceptibility, perhaps to gynecological issues in general. Women who felt anxious or worried about cancer or the test result also perceived themselves as more susceptible to an abnormality (which need not to be a realistic risk appraisal), and were more likely to take own their initiative to a Pap smear. Anxiety may thus lead to a self-protective behavior, causing them to try to reduce their anxiety by having a Pap smear.

There is, however, also another possibility, and that is that non-attenders and attenders do not differ in experienced anxiety, but in the way in which they try cope with it. Although the anxiety among attenders work as a cue-to-action to have a Pap smear, non-attenders might try to cope with the anxiety by avoidance and denial involving minimizing the seriousness of the disease (Lerman et al., 1996). Furthermore, non-attenders in our study did not perceive cervical cancer to be as severe as did attenders. This may indicate that the non-attenders try to reduce the threat by minimizing the seriousness of cervical cancer.

The answers to open-ended questions about future intentions did indicate that a small group of the non-attenders would not attend because they felt anxious about the test or the examination, as was also found by others (Bergmann et al., 1996; Elkind et al., 1988; Nathoo, 1988). For these women, anxiety worked instead as a barrier to attend, causing them to try to avoid situations where their anxiety was likely to increase.

6.2.2.7 Benefits and barriers (Paper III)

Non-attenders did not perceive the Pap smear to be as beneficial as did attenders and expressed more barriers to attend. This is well in line with results from other studies (Glasgow et al., 2000; Hill et al., 1985; King, 1987; Lantz et al., 1997; Orbell et al., 1995; Peters et al., 1989). The results indicate that “peace of mind” is an important benefit, which is also strengthened by the interaction between time-consuming barriers and anxiety. Women who were anxious or worried about cancer, or about the results of a Pap smear, had no difficulties to give priority to the test.

Women with economical barriers, who encountered “other problems”, were also more likely to be non-attenders and reported low levels of social support (which may be an important resource for coping). These women might perceive a Pap smear as “something else to add to their list of problems”(Nathoo, 1988). Possibly these women tried to justify their non-attendance considering the Pap smear unnecessary in the absence of symptoms. Non-attenders kept holding on harder to their preferences than did attenders in stating that they would not participate if their preferences were not met, preferences that may have to do with convenience, belief in better service, and reduction of embarrassment (Elkind et al., 1988).

Therefore it is not only important to provide information about the value of having a Pap smear, but also to contradict barriers and to make it as easy as possible for women to have a Pap smear.

Emotional barriers did not affect attendance status after controlling for other variables in our study. This discrepancy with some other studies (Lantz et al., 1997; Murray et al., 1993:b; Orbell et al., 1995) might be an effect of the objective measure of attendance status, including women perceiving themselves as non-attenders as well as women who did not. The former group actually showed the stronger barriers in our study and they also experienced emotional barriers. Some non-attenders also perceived themselves as non-attenders, with stronger barriers, whereas others perceived themselves as attenders. The beliefs of the latter group were very much alike those of the true attenders, except that they did not perceive the Pap smear as beneficial. These women could probably be convinced to participate more often through relevant information about Pap smear screening. The group of non-attenders who also self-reported as non-attenders might be harder to convince, especially if they had not had a Pap smear for a long time.

Perceived barriers became stronger with time and the anticipated embarrassment or pain among women who never had a Pap smear may be greater than what they actually experience when they have the smear (Burak et al., 1997; Hesselius et al., 1975). That is, the women having the greatest cause to attend also had the strongest barriers.

To overcome emotional and other barriers, intensive workup through gynecologists and establishment of personal contacts might be a way to achieve higher participation among these women.

6.2.3 Increasing attendance at Pap smear screening (Paper IV)

Many of the differences between non-attenders and attenders in attitudes and constraints (Paper II-III) might be remediable through relevant information or education about the benefits of Pap smear screening, given that women who do not participate in screening are receptive to such information.

6.2.3.1 Modified intervention

Since the general knowledge among women about the purpose of the Pap smear was poor, and since the non-attenders did not find it as beneficial as did attenders, we hypothesized that increased knowledge would also increase attendance. However, the additional information that was enclosed in the standard invitation did not show any convincing effect. We pondered why a substantially modified invitation letter did not improve participation in our study. Although women over a certain age are more attentive to written information, it is likely that specific information is needed for women who are invited to screening for the first time. In previous studies, higher attendance was achieved by increasing knowledge, through mail-outs, direct contact, or educational programs. Most studies were, however, performed in settings with no organized screening and on subgroups of women. These studies indicate that increased knowledge is an effective measure to increase attendance, perhaps especially so in settings where the initiative to have a Pap smear mainly lies with the woman.

The modified information did, however, show a small positive long-term effect on attendance. Whether this effect will prove to be consistent even after a longer time period or whether it will diminish after a while, as do the effects of television, radio and magazine campaigns (Shelley et al., 1991), remains to be seen.

6.2.3.2 Reminder letters

To serve those women with temporary barriers to attendance, women who had not attended after the first invitation were randomized to receive a reminder letter. The reminder letter increased attendance substantially, most strongly among women who had had a prior smear and among women who had not received social welfare. Overall, the effect seemed to be stronger among women from higher socio-economic strata. A reminder letter is a cost-effective measure, since it adds relatively little cost and definitely improves the overall attendance rate. In an existing call-recall system it should not be difficult to implement as a recurrent routine.

6.2.3.3 Phone reminder

As a last step women who had not attended after a reminder letter were randomized to receive a phone reminder. This was to give women an opportunity to ask questions about the Pap smear and to schedule an appointment directly. The phone reminder definitely showed the strongest effect on compliance of the three tested interventions. The strong relative and absolute effect of a phone reminder agrees with one earlier study on attendance at mammography (Taplin et al., 2000), and a study on the combination of a physician reminder letter and a phone contact (Lantz et al., 1995). The phone reminder showed a somewhat lower effect on women aged 24-29 years, women who had not had a prior smear, who were on social welfare, or nulliparous. However, the effect may have been underestimated in these groups, since they were overrepresented among women who could not be reached by a phone reminder. In our experience, women perceived the phone reminder favorably because an appointment could be scheduled directly and questions answered. A positive effect has also been shown in studies among minority groups by offering on-site screening when visiting a clinic or a hospital (Ansell et al., 1994; Mandelblatt et al., 1993:b; Margolis et al., 1998; White et al., 1993). A personal contact might also be important, especially for women who feel anxious about the examination or the Pap smear. The possibility to have the Pap smear taken by the person you talked to might further increase motivation.

6.2.3.4 Cumulative effects

The number of women participating in Pap smear screening was almost doubled and the number of detected cytologic abnormalities more than tripled. Hence, additional efforts to increase attendance seem to reach those in greatest need of screening. However, if the interventions should be implemented as a regular policy, this effect could not be expected to continue, since the high prevalence of cytological abnormalities would decrease. In fact, this is the goal of Pap smear screening itself.

6.3 IMPLICATIONS FOR FUTURE RESEARCH

6.3.1 Interventional strategies

In this thesis we have investigated compliance in two areas of major importance for disease prevention; namely, compliance to a postal questionnaire and compliance at screening for cervical cancer. We also succeeded to increase compliance in both areas.

6.3.1.1 *Compliance in epidemiological research (Paper I)*

The reported response in epidemiological studies has not decreased over a period of 20 years (Olson, 2001). This may be somewhat surprising, since one can assume that people today are tired of being regarded as potential consumers/buyers/contributors at home and have become refractory to more information of any kind. One reason could be that the topic nevertheless concerns many people and motivates them to make a contribution. However, many people do not respond, which in turn can introduce a bias. Additional efforts to increase compliance can, however, reduce the magnitude of this bias (Brambilla et al., 1987; Richiardi et al., 2002).

The use of combinations of many manipulative aspects rather than one single technique is an effective way to increase the response rate to postal questionnaires. Although additional efforts to increase the response rate may lead to a higher partial non-response, the possibility for complementary phone interviews does exist.

To send a preliminary notification was an easily implemented and successful method to increase the response rate, whereas the questionnaire length did not seem to have an important impact. Rather than reducing length, more effort should be devoted to making the questionnaire easy to understand and to answer.

An additional interventional strategy that has proven to give a successful outcome is reminders (perhaps especially with an additional questionnaire or by phone). This is in fact one of the advantages of the postal questionnaire, that it allows the investigators to send repeated reminders if the initial response rate is low. One should, however, be aware that some methods used to increase response, such as incentives, may instead introduce a bias, since they motivate different strata of the population (Marrett et al., 1992; Parkes et al., 2000). These methods can probably work if they are used carefully.

The response rate differed among different strata of the population. This might be remediable by making the questionnaire interesting to the participants by explaining how the study concerns them. Moreover, since participation in an important study may even be perceived as beneficial (Taylor et al., 1991), the aim of the study and the value of the individual contributions should be emphasized. Also, the researchers should try to reduce the costs of complying, for example, by including a return envelope and names and telephone numbers of contact persons.

Lastly, the most important thing in epidemiological research may not be to design interventional strategies, but to maintain trust. Upon participating in a study the respondents rely on us that the security is high, that the study is of major importance and that their responses will be presented in a nice way. Distrust could affect

compliance far more negatively than all efforts to increase attendance could compensate for.

6.3.1.2 Compliance in medical screening (Paper II-IV)

Cervical cancer is one of the most preventable diseases, owing to condom use, earlier detection and treatment of precursor lesions to cervical cancer, and perhaps vaccination against HPV in the future.

Interventions through a reminder letter and a phone reminder to non-attenders at organized Pap smear screening do increase the attendance. The reminder letter is an effective and cost-effective measure and should be easy to implement in an organized screening program. The phone reminder was even more effective, but may be more difficult to implement. Phone reminders might be used for women who have not participated during a long time period. The personal contact and the ability to schedule an appointment directly by phone are probably important motivators for these women.

An additional interventional strategy is increased information about the preventive measures available for cervical cancer, especially information on the benefits of the Pap smear, the significance of a normal smear, and the preventive effect of condom use. The added information did not have the positive effect we hoped for in our study. Alternative ways to distribute information is through a mailing prior to the invitation. This allows more detailed information to be given, allowing the women to evaluate and make a decision about the Pap smear when no direct action is required. Another important source of information is communication with gynecologists, midwives and physicians, through information brochures in the waiting rooms and by a personalized letter from the woman's general practitioner. To be advised by a doctor (or a midwife) can both be an important cue-to-action and an opportunity to increase satisfaction with health care and understanding of the importance of Pap smear screening.

Another interventional strategy is to facilitate participation in the test. If pre-scheduled appointments are not used, it should be made easy to reach the Pap smear site by phone to make an appointment. Another possibility would be to schedule appointments via the Internet. Walk-in clinics with receiving hours after work might also make it easier for many women to have the Pap smear.

6.3.2 Additional questions

The results of the studies described in this thesis give rise to additional issues that need to be resolved in future research.

We need to know more about the youngest women's perception and knowledge about Pap smear screening and to determine whether special motivation is required for this group. Since the risk of developing cervical cancer increases with increasing age at the first Pap smear (Sparén, 1996), it is highly important that women start screening when recommended.

Greater insight into how to induce women with high barriers and anxiety feelings to attend Pap smear screening is needed.

Additional investigations of the best way to spread information about the Pap smear are also needed, as well as an investigation of the potential effect that knowledge about the route of transmission of HPV could have on attendance and on the women's reactions to an abnormality.

Further investigations of how to make the Pap smear as available as possible to women living in rural areas and with practical barriers (Papers II-III) and of the possible effect of pre-scheduled appointments versus scheduling one's own appointment.

Investigations of reasons for non-attendance among immigrant women, and exploration of the possible relation between culture and preventive health care is another important area of future research.

Research about the magnitude of adherence to follow-up and treatment of an abnormal Pap smear might be important to fine-tune the screening organization, since late stage disease diagnosis may be a result of inadequate follow-up of abnormalities found at screening (Marcus et al., 1992; Michielutte et al., 1994).

7 CONCLUSIONS

- Simple modifications of the mailing strategies do affect the response rate to postal questionnaires. The combined effects of simple modifications in mailing routines and in the appearance of the questionnaire may be of decisive importance for the success of an epidemiological study (Paper I).
- Special measures to attain a high response rate may be required among young and very old people, men and city dwellers (Paper I).
- The partial non-response increased with increasing response rate, although the moderate losses due to partial non-response did not outweigh the overall gains produced by the mailing modifications (Paper I).
- Self-reported attendance is not a valid measure of true attendance. As many as 57% of the non-attenders underestimated the time since their last smear (Paper II).
- Some demographic discrepancies may exist between attenders and non-attenders at Pap smear screening; the youngest women, women living in rural areas and immigrated women are less likely to attend screening (Paper II and IV). Socioeconomic status had no impact on attendance after controlling for potential confounders (Paper II).
- Gynecological visits for other reasons, visiting the same gynecologist, the women's own activity in order to have a Pap smear and knowledge of the recommended screening interval are important predictors of attendance (Paper II).
- Insufficient prior attendance is a strong predictor of non-attendance (Paper IV). Although sexual risk behavior had no impact on attendance, the non-attenders were more likely to protect themselves with condoms during intercourse (Paper II).
- Important differences in attitudes and beliefs about Pap smear screening exist between non-attenders and attenders to cervical cancer screening (Paper III).
 - Perceived time-consuming and economical barriers are negatively associated with attendance
 - Perceived benefits, anxiety, and severity are positively associated with attendance
 - These relations were strengthened with increasing time since last smear or if self-reported attendance status was used as outcome instead of actual attendance.
- Simple modifications of the invitation and the call-recall system can drastically increase the compliance at Pap smear screening, especially a written reminder and a phone reminder (Paper IV).
- Interventions may encourage women at high risk of cervical cancer to attend more than other women, since the number of detected cytologic abnormalities increased more than the participation rate (Paper IV).

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