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Three birds with one stone: a protocol for a randomised intervention study to increase participation in cervical and colorectal cancer screening among women attending breast cancer screening

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ABSTRACT

Introduction The participation rate is higher in breast cancer screening than in cervical cancer (CCU) and colorectal cancer (CRC) screening. In this cluster-randomised study, we aim to evaluate an intervention offering home-based CCU and CRC screening to women when attending breast cancer screening if they are overdue for CCU and/or CRC screening.

Methods and analysis On intervention days, one of the five breast cancer screening units in the Central Denmark Region will be randomly allocated to intervention, whereas the remaining units will serve as control. Women attending breast cancer screening in the intervention unit will be offered information regarding their CCU and CRC screening history, and, if overdue, they will be offered self-sampling screening kits. For CCU screening, women aged 50–64 years will be offered a vaginal self-sampling kit for human papillomavirus testing. For CRC screening, women aged 50–69 years will be offered a kit to obtain a faecal immunochemical test. Women attending the control units will receive only standard care.

After the intervention, a survey will be sent to all women in the intervention and control group, asking about their experience while attending breast cancer screening. Primary outcomes will be difference in the coverage in CCU and CRC screening 6 months after intervention between the intervention and the control group, and difference in participation rates 6 months after intervention for those who were overdue for CCU and/or CRC screening at the time of the intervention.

Ethics and dissemination The project is listed in the record of processing activities for research projects in the Central Denmark Region (R. No.: 1-16-02-217-21). According to the Danish Consolidation Act on Research Ethics Review of Health Research Project, this study was not notifiable to the Committee (R. No.: 1-10-72-1-21). The findings will be disseminated in peer-reviewed scientific journals.

Trial registration number NCT05022511.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ To our knowledge, this study will be first of its kind to offer self-sampling kits to women who are overdue for their CCU and CRC screening when attending breast cancer screening.
⇒ A strength of this study is the large study population randomly allocated to the intervention or the control group, minimising the risk of confounding.
⇒ The study will be conducted within the Danish screening programme. This makes the study design reliable and easy to implement in case of a positive result, while introducing a potential limitation since current national guidelines might be updated, and in this case the study protocol would need to be changed accordingly.

INTRODUCTION

Since 2003, the European Union Council has recommended organised, population-based screening for breast cancer, cervical cancer (CCU) and colorectal cancer (CRC) using mammography, cervical cytology or human papillomavirus (HPV) test and guaiac or immunochemical faecal occult blood test (FOBT), respectively.[1] The three screening programmes have been widely implemented across Europe.[2] However, most of the screening programmes suffer from suboptimal participation rates, decreasing their effectiveness. European CRC screening programmes using the faecal immunochemical test (iFOBT, in the following termed FIT) have participation rates of 23–71%[3]; breast cancer screening programmes, 13–85%[4]; and CCU screening programmes, 40–85%.[5]

Common strategies to improve participation across the three programmes have been identified at an individual level (eg, postal or telephone reminders, general practitioner's signature on the invitation letter, education), at a population level (eg, mass media campaigns) and at the health service management level (eg, scheduled appointments,

mobile mammography, HPV self-sampling).[6–8] Despite such initiatives, participation in cancer screening is often suboptimal.

In Denmark, the participation rate after invitation in breast cancer screening exceeds 80%,[9] which is above the 61% recorded for both CCU[10] and CRC screening.[11] Thus, attending breast cancer screening provides an opportunity for personal communication with the women regarding their screening status in CRC and CCU programmes. Furthermore, a UK study revealed that women are potentially interested in this approach.[12] However, it has yet to be explored whether this holds potential to increase participation in the two screening programmes with the lowest participation rates.

The aim of this study will be to increase participation in CCU and CRC screening programmes in Denmark by offering home-based CCU and CRC screening to women attending breast cancer screening if they are overdue for one or both screening programmes.

METHODS AND ANALYSIS

Setting

In Denmark, women aged 50–69 years are entitled to biennial breast cancer screening by mammography. The women receive a digital invitation with a prebooked appointment at a screening unit.[13] If the woman fails to attend the prebooked appointment, a reminder is sent shortly after.

Women aged 23–64 years are offered CCU screening. From the age of 50 years, they receive an invitation every fifth year via digital mail encouraging them to book an appointment with their general practitioner (GP) to have a cervical sample taken. Non-participants receive up to two reminders 3 and 6 months after the initial invitation.

All residents aged 50–74 years are offered biennial screening for CRC with FIT. They receive a kit for self-sampling by mail including written instructions and pictograms explaining how to collect the sample, an informational pamphlet and a prepaid, pre-addressed return envelope to return the sample. A reminder is sent 6 weeks after the initial invitation if no sample has been examined.

In all three screening programmes, non-participants receive a new invitation if they remain in the screening-eligible age range when due for screening again, unless they have actively unsubscribed from the programme.

In Denmark, five regions manage primary and secondary healthcare services, which are tax-funded, free-access services for all residents. The Central Denmark Region accounts for approximately 1.3 million inhabitants corresponding to roughly one-fourth of the Danish population.[14] The three population-based cancer screening programmes are based on national guidelines and administered in each of the five regions.

Communication between residents and public authorities, including the healthcare systems, is mainly through secure, digital mail, whereas residents with exemptions

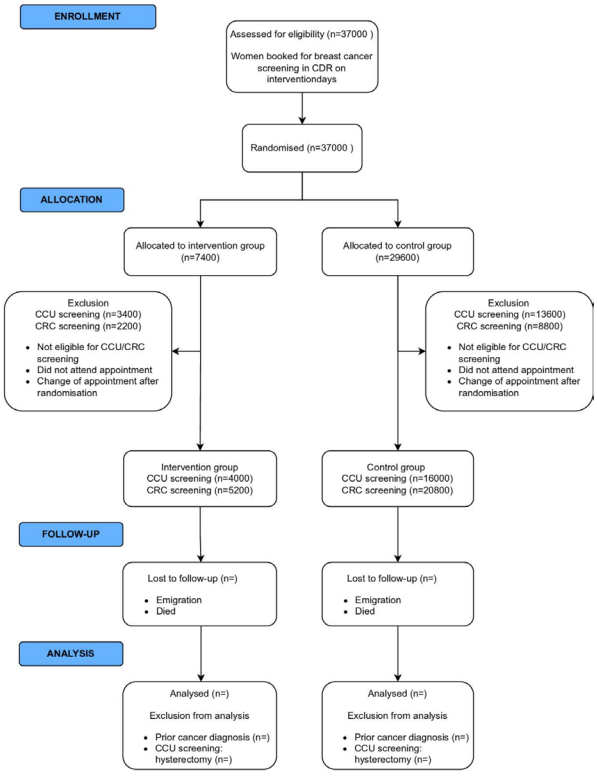

Figure 1 Consolidated Standards of Reporting Trials 2010 flow diagram of the study for primary outcomes. CCU, cervical cancer; CDR, Central Denmark Region; CRC, colorectal cancer.

from digital mail receive surface mail. This group accounts for 6.3% of the Danish population (both sexes) in the age range from 45 years to 75 years.[15]

Study design

This study will be a cluster-randomised controlled trial conducted in the Central Denmark Region where five breast cancer screening units serve women 5 days a week. All five units will be included in the study and will be randomised to an equal amount of intervention days. On the intervention days, the other four units will serve as the control group, providing a randomisation ratio of 1:4 (figure 1). Randomisation will be conducted by a data manager using a pseudorandom number function in the statistical software Stata V.16.

The study will comply with the Standard Protocol Items: Recommendations for Interventional Trials statement.[16]

Study population

The population will comprise women aged 50–69 years attending breast cancer screening in the Central Denmark Region on intervention days. The study will include women invited for breast cancer screening at 69 years who, due to postponement, have turned 70 years at their appointment.

In CCU screening, women aged 50–64 years will be classified as overdue if they have never participated, if they have no record of a cervical sample in the past 5 years and

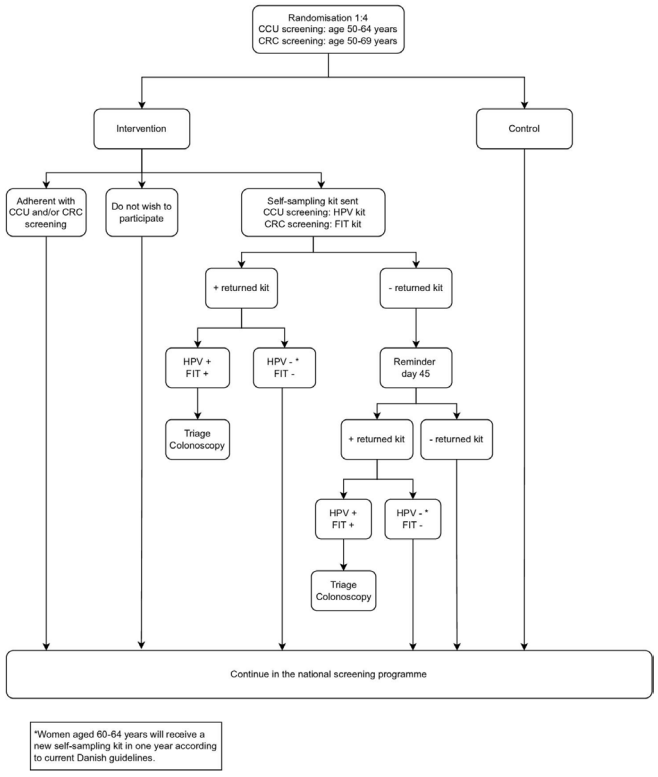

Figure 2 Flow diagram of the intervention. CCU, cervical cancer; CRC, colorectal cancer; FIT, faecal immunochemical test; HPV, human papillomavirus.

6 months or if they were non-responders to a screening invitation received more than 6 months ago.

In CRC screening, women aged 50–69 years will be classified as overdue if they have no record of a FIT in the past 2 years and 4.5 months, or if they have not responded to an invitation received more than 4.5 months ago. The time intervals were chosen to ensure that the women have had time to receive both an invitation and the first reminder without responding after a 3-month interval.

Intervention

Figure 2 summarises the intervention. On intervention days, a research assistant will be available in one of the five screening units in the Central Denmark Region, asking women attending breast cancer screening if they are interested in having a check-up on their CCU and CRC screening status. If oral consent is obtained, the research assistant will check their screening status in the administrative register of each of the screening programmes.

Women who are overdue for CCU screening will be offered to receive a self-sampling kit by mail or reminded to call their GP to have a cervical cytology sample taken, depending on their preference. If a woman prefers a self-sampling kit, she will receive a dry brush for vaginal self-sampling (Evalyn Brush from Rovers Medical Devices, Netherlands),[17 18] written and picture-based user instructions on how to collect the sample, the national information pamphlet for CCU screening and a prepaid, pre-addressed envelope for returning the sample. A reminder will be sent 6 weeks after dispatch of the self-sampling kit if no sample has been returned. The vaginal self-samples will be analysed for high-risk HPV (HPV16, HPV18 and 12 other high-risk HPV types in one pool; HPV 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68) using the Cobas 4800 HPV DNA test (Roche Diagnostics, Switzerland),[19] at the Department of Pathology, Randers Regional Hospital, according to routine laboratory protocols. Follow-up will be according to nationally decided procedures.

In the national CRC screening programme, everyone who is overdue for CRC screening may order a new screening kit. If a woman in the present study is overdue for CRC screening, we offer to order a new self-sampling kit for her, which she will then receive by mail. The package sent to her will contain a self-sampling kit for FIT (OC Sensor System, Eiken Chemical Company, Japan), instructions on how to collect a sample, the national information pamphlet for CRC screening and a prepaid, pre-addressed return envelope. A reminder will be sent 6 weeks after dispatch of the self-sampling kit if no sample has been returned. The samples will be analysed for haemoglobin with a cut-off value of 100 ng haemoglobin (HB)/mL buffer. Follow-up will be conducted according to the standard procedure in the national CRC screening programme.

If the woman accepts a self-sampling kit for CCU and/or CRC screening, she will be informed—orally at the breast cancer screening unit and in the written material—that she will subsequently receive the result of the test(s) by digital mail, and a copy of the result will be sent to her GP.

The women in the control group receive only the standard screening offers forming part of the national screening programmes.

The women in the study population will receive a survey within few days after having attended breast cancer screening asking about their experience with breast cancer screening. The survey will include questions on their general experience with the visit attended in the screening unit. Additionally, the women in the intervention group will be asked if they find it acceptable to be asked about participation in the two other screening programmes when attending their breast cancer screening visit.

Clinical management

If a woman returns a vaginal self-sample for HPV testing, she and her GP will receive the result of her test by digital mail within 3 weeks after the completed test has been returned. If the sample is HPV positive, the woman will be advised to see her GP within 1 month for an additional gynaecological examination at which a cervical cytology sample is collected. The GP-collected sample will be analysed for HPV, undergo microscopy and will be classified according to the Bethesda system.[20] The GP is responsible for further clinical management according to national screening guidelines. If no cervical sample from an HPV-positive woman has been examined after 90 days, one reminder to book an appointment at the GP will be sent by digital mail.

If the self-sample is HPV negative, follow-up will be conducted according to age and screening history. HPV-negative women aged 50–59 years will be referred back to the national screening programme. Women aged 60–64 years who have a normal cervical sample within the past 6 years will exit the screening programme. Women aged 60–64 years without a normal cervical sample within the past 6 years will be re-invited within 12 months to do an additional self-sample for HPV before they exit the programme. This is according to new guidelines on HPV self-sampling in Denmark for women aged 60–64 years.[21] If the self-sample is invalid, the woman will be advised to see her GP for a cervical sample.

If the woman returns a self-collected FIT, she will receive the result by digital mail and the GP will also receive the result within 2 weeks from returning the completed sample. Follow-up is conducted according to the national screening programme.[22] Thus, if the FIT is positive for traces of blood, the woman will be contacted by surface mail with a prebooked appointment for colonoscopy within 14 days at a hospital-based screening endoscopy unit. If the woman does not show up for the colonoscopy, she will be reminded twice by digital mail and once by telephone with advice to book a new appointment. If the FIT is negative, the woman will be referred back to the national screening programme through a new invitation sent out 2 years later. If the test is invalid, a new test kit is sent to the woman.

Since the study is nested within national cancer screening programmes, the clinical management strategies used in the study must adhere to national guidelines. If the current national guidelines are updated during the study period, details relating to the study may be changed accordingly, and the project leader will be responsible for passing on the information to relevant partners.

Outcomes

Main effect measures

1. Difference between the control and the intervention group in overall coverage of CCU (self-sample or cervical cytology sample) and/or CRC (FIT) screening 6 months after the visit in the breast cancer screening unit measured as the proportion of women adherent with CCU and/or CRC screening for the past 3.5/5.5 years according to age for CCU screening and the past 2 years and 4.5 months for CRC screening.
2. Difference between the control and the intervention group with respect to CCU (self-sample or cervical cytology sample) and/or CRC (FIT) screening participation 6 months after the intervention for the women who are overdue for CCU/CRC screening at the intervention date.

Secondary outcomes

Among the women who are overdue for CCU screening, the secondary outcomes will be prevalence of HPV in vaginal self-samples, compliance with follow-up in HPV-positive women (timely follow-up will be reported as a GP-collected cervical sample within 180 days from the HPV-positive sample), screening history of self-samplers ('under-screened' defined as screened at least once with a cytology sample within the 10 years leading up to the inclusion date, but not screened within the past 5 years and 6 months, 'un-screened' defined as no cytology sample registered within the past 10 years), referral rate for colposcopy, incidence of cervical intraepithelial neoplasia of grade 2+ (CIN2+) (including CIN2, CIN3/adenocarcinoma in situ and carcinoma), incidence of HPV-positive cases in women 60–64 years after 12 months with an initial negative HPV sample.

For those who are overdue for CRC screening, secondary outcomes will be prevalence of positive FIT cases, compliance with follow-up (timely follow-up will be reported as colonoscopy within 60 days from a positive FIT), screening history of women who receive a new FIT ('under-screened' defined as a minimum of one FIT, but no FIT within the past 2 years and 4.5 months, 'un-screened' defined as no previous FIT despite invitation) and histology (adenomas and cancer).

Participation after subsequent screening invitation in all three cancer screening programmes 5 years after the intervention may be measured.

Process outcomes

In the intervention group, process outcomes will be the proportion of women accepting a check-up on their CCU and CRC screening status, the proportion of women overdue for CCU and/or CRC screening, the proportion of women accepting a test kit and the proportion of women not returning the kit.

The surveys sent to the women after inclusion will be used to evaluate the acceptability of the intervention and the participants' satisfaction with the breast cancer screening.

Other variables

Outcomes to test if the randomisation succeeded will be screening history, previous cancer diagnoses, hysterectomy, inflammatory bowel disease (IBD) and socioeconomic data (age, ethnicity, marital status and educational level).

Sample size

Preliminary data from a study of the proportion of women participating in one, two or all three Danish cancer screening programmes show that approximately 20% of women participating in breast cancer screening did not participate in CCU screening (excluding women with hysterectomy or a Charlson comorbidity score ≥3), and approximately 35% did not participate in CRC screening (excluding women with a previous diagnosis of CRC or a Charlson comorbidity score ≥3) (unpublished data).

The premise is to attend each breast cancer screening unit 20 times, corresponding to a total of 100 intervention days. Every unit has prebooked approximately 74 women daily of whom 55 are expected to attend. Assuming that

40 women per day are eligible for CCU screening and 52 for CRC screening, leaving a study population of 4000 and 5200 women, respectively, the study may detect a difference in screening coverage as low as 2.3% in CCU screening (increasing from 80% to 82.3%) and 2.4% in CRC screening (increasing from 65% to 67.4%) with a risk of type 1 error of 5% and type 2 error of 10% (power of 90%). In the analyses, women who have had hysterectomies and/or CCU/CRC will be excluded.

A design effect due to cluster randomisation is not taken into account as the intervention will be equally distributed between the screening units over the entire study period. The individuals within the clusters are considered independent of each other.[23]

Enrolment was initiated in September 2021 and is expected to go on for 1 year.

Data sources

The study population will be identified in the regional administrative system of the breast cancer screening programme. On intervention days, the current status of participation in CCU screening will be obtained from the Danish Pathology Register (DPR), which holds data on cervical cytology samples in Denmark.[24] Furthermore, the current status of participation in CRC screening will be obtained from the Invitation and Administration Module, which holds data on FIT in Denmark.

Data on test results from cytology, HPV test, colposcopies and screening history in CCU screening will be retrieved from the DPR and the Danish CCU Screening Database.[25] Data on screening history in CRC screening and data on FIT result, colonoscopies and histology will be retrieved from the Danish CRC Screening Database.[26]

Furthermore, data on previous cancer diagnoses will be drawn from The Danish Cancer Registry[27] and The Danish National Patient Register[28] which will also provide data on IBD and total hysterectomies (codes are provided in table 1).[29]

Statistics Denmark will provide sociodemographic data.[30] Using Statistics Denmark's classification, ethnicity will be categorised by country of origin as either Danish, Western (European Union, Andorra, Australia, Canada, Iceland, Liechtenstein, Monaco, New Zealand, Norway, San Marino, Switzerland and the USA) or non-Western (others). Marital status will be classified as cohabitating or living alone. Highest educational attainment will be classified according to UNESCO's classification as low (≤10 years), middle (11–15 years) or higher education (> 15 years).

The study cohort will be managed in REDCap (Research Electronic Data Capture), which is a secure web application for building and managing online surveys and databases.[31] All data will be linked at the individual level using the unique 10-digit CPR number assigned in Denmark at birth or on emigration.[26]

Statistical analyses

Baseline characteristics in both groups will be presented using descriptive statistics (number and proportions) to determine if the randomisation was equally balanced.

Differences in coverage and participation rates between the intervention and the control group will be estimated both as absolute difference and relative risk with 95% CIs.

Secondary and process outcomes will be reported by descriptive statistics including 95% CIs.

All statistical analyses will be conducted using Stata V.16.

In case shewed selection is detected due to cluster randomisation, adjusted analyses will be performed for relevant confounders.

Patient and public involvement

The study design was pilot tested for feasibility and acceptability, the latter including women attending the breast cancer screening unit at the days of pilot testing. These women were asked to share their experience with the intervention. The responses were analysed to ensure participant satisfaction with the intervention. Other than this, neither patients nor the public will be involved in this research. We plan to disseminate the results to the general screening population and patient organisations through mass media.

ETHICS AND DISSEMINATION

According to the EU's General Data Protection Regulation (Article 30), this project is listed in the record of

Table 1 International Classification of Diseases (ICD) codes used to identify previous cancer diagnoses, total hysterectomies and irritable bowel disease

	ICD-7/8	ICD-10
Colorectal cancer	153.x, 154.x, 253.x, 453.x, 454.x, 653.x, 654.x, 753.x, 754.x, 853.x, 854.x	C18-20
Cervical cancer	171.x, 671.x, 771.x, 871.x	C53
Hysterectomy	ICD-8 (1977–1995) surgical procedure codes: opr61050, opr61020, opr72230, opr61040, opr72650, opr61100, opr72240, opr61780, opr62300	ICD-10 surgical procedure codes: KLCD00, KLCD01, KLCD04, KLCD10, KLCD11, KLCD30, KLCD31, KLCD40, KLCD96, KLCD97, KLDC10, KLDC13, KLDC96, KLDC20, KLDC23, KZXX00, KMCA33, KLEF13, KLEF00B
Irritable bowel disease		DK50-51

Note: Danish Cancer Register used ICD-7 and Danish National Patient Register used ICD-8.

processing activities for research projects in the Central Denmark Region (R. No.: 1-16-02-217-21). Under the Consolidation Act on Research Ethics Review of Health Research Projects, Consolidation Act number 1083 of 15 September 2017, Section 14 (2), notification of medical database research projects to the research ethics committee system is required only if the project involves human biological material. Thus, this study was not notifiable to the Committee (R. No.: 1-10-72-1-21). Accordingly, information may be retrieved from regional administrative systems and registers without informed consent from the participants when approved by the hospital management. The hospital management at Randers Regional Hospital, Central Denmark Region, has approved this project. The study is registered with ClinicalTrials.gov (see table 2 for the WHO Trial Registration Data Set) and will be conducted in accordance with the Good Clinical Practice guidelines.

The results will be reported in international peer-reviewed scientific journals and compiled as a thesis,

Table 2 All items from the WHO Trial Registration Data Set

Data category	Information
Primary registry and trial identifying number	ClinicalTrials.gov, NCT05022511
Date of registration in primary registry	10 August 2021
Secondary identifying numbers	N/A
Source(s) of monetary or material support	University Research Clinic for Cancer Screening and the Department of Public Health Programmes, Randers Regional Hospital, Denmark
Primary sponsor	University Research Clinic for Cancer Screening and the Department of Public Health Programmes, Randers Regional Hospital, Denmark
Secondary sponsor(s)	Department of Clinical Medicine, Aarhus University, Denmark
Contact for public queries	Anne Dorte Lerche Helgestad, MD (annesper@rm.dk)
Contact for scientific queries	Anne Dorte Lerche Helgestad, MD University Research Clinic for Cancer Screening and the Department of Public Health Programmes, Randers Regional Hospital, Denmark
Public title	Three birds with one stone
Scientific title	Three birds with one stone: a randomised intervention study to increase participation in cervical and colorectal cancer screening among women attending breast cancer screening
Countries of recruitment	Denmark
Health condition(s) or problem(s) studied	Cervical cancer and colorectal cancer screening
Intervention(s)	Active comparator: An offer to receive information on screening status in cervical and colorectal cancer screening when attending breast cancer screening. If overdue for one or both screening programmes, self-sampling screening test(s) is/are offered.
	Control comparator: Standard screening offers according to the national screening programmes.
Key inclusion and exclusion criteria	Ages eligible for study: 50–64 years (cervical cancer screening), 50–69 years (colorectal cancer screening) Sexes eligible for study: Women Accepts healthy volunteers: No
	Inclusion criteria: Women aged 50–69 years booked for a breast cancer screening on an intervention day
	Exclusion criteria: Not eligible for cervical or colorectal cancer screening, did not attend breast cancer screening, changed appointment for breast cancer screening after randomisation, insufficient Danish skills to provide informed consent
Study type	Interventional
	Allocation: Cluster randomised intervention model. Parallel assignment 1:4.
	Primary purpose: Prevention
Date of first enrolment	September 2021
Target sample size	37 000
Recruitment status	Recruiting
Primary outcome(s)	1. Difference between intervention and control group with respect to coverage in cervical cancer/colorectal cancer screening 6 months after the intervention. 2. Difference between the intervention and the control group in proportion of women participating in cervical cancer and colorectal screening after 6 months for women who were overdue for their cervical cancer/colorectal cancer screening at the intervention.
Key secondary outcomes	For both cervical and colorectal cancer screening, secondary outcomes will be screening-related outcome, clinical follow-up, satisfaction with breast cancer screening during intervention and process outcomes.

which will be submitted for examination for a PhD at Aarhus University, Denmark. Furthermore, results will be presented at national and international scientific meetings and disseminated to healthcare stakeholders, patient organisations and the general public through press releases.

Perspectives

To our knowledge, this study will be the first of its kind to offer an interprogramme collaboration between three cancer screening programmes simultaneously by reaching out to women overdue for CRC and/or CCU screening when participating in breast cancer screening. By reducing logistic challenges and taking advantage of a more personalised communication with the women, this study may enhance participation in unscreened and underscreened women who have not deliberately chosen not to participate. These women are presumably susceptible to preventive healthcare but for a host of reasons end up as non-participants. Women who do not participate in breast cancer screening must be targeted by other interventions.

A strength of this study is that it is an easily scalable intervention, which—in case of a positive result—has the potential to be implemented in the national screening programme at the breast cancer screening units without great costs.

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Contributors ADLH is the principal investigator of the study and responsible for the coordination of the trial with supervision from MBL and BA. ADLH, MBL and BA are primarily responsible for the study design with input from SN, MT and LKP. MT and LKP contributed advice and knowledge on cervical cancer (CCU) screening, follow-up after CCU screening and self-sampling. SN contributed advice and knowledge on colorectal cancer (CRC) screening, follow-up after CRC screening and statistical considerations. ADLH drafted the manuscript. All authors contributed with further development of the manuscript and reviewed and approved the final version.

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Competing interests Roche Diagnostics sponsors the Cobas 4800 HPV DNA tests. According to the contract between Roche Diagnostics and the University Research Clinic for Cancer screening, the Department of Public Health Programmes, Randers Regional Hospital, Roche Diagnostics has no influence on the scientific process and no editorial rights pertaining to this manuscript. MT, LKP and BA have participated in other studies with human papillomavirus (HPV) DNA tests sponsored by Roche Diagnostics. MT has received honoraria from Roche Diagnostics for lectures on HPV self-sampling. SN has received a speaking fee from Norgine and LKP has received speakers fee from AstraZeneca and MSD.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Under Danish law, restrictions will apply to the availability of the data generated during this study. Register data will be used under a license for the present study and may be available upon reasonable request to the Danish Health Data Authority and Statistics Denmark. The participants will not be asked to provide consent for publication of the questionnaire data, but data may be available in anonymous form from the corresponding author upon reasonable request.

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