

Norway – a retarded country close to 20 years since EU recommended colorectal cancer screening? A failure or a success?

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Norway has one of the world's highest incidence rates for colorectal cancer (CRC) – and it is increasing. The CRC incidence rate has more than doubled since World War II – much more than in any of the other Nordic countries [1]. There is limited knowledge about the reasons for this increase, which has made population screening and further research on etiology and exploration of primary preventive measures particularly interesting.

In Norway, a national screening programme for cancer of the cervix has existed since 1995 and for breast cancer since 2005, with 69% and 76% attendance rates, respectively [2,3]. Programmatic CRC screening has been recommended since 2003 for EU member states [4] – many of them with lower incidence rates than Norway, poorer compliance for screening in general, and with less resources. A national CRC screening programme will, however, be launched in Norway in 2022 – starting with roll-out of biennial immunochemical fecal occult blood testing (FIT) and gradually converting to colonoscopy as the primary screening method when sufficient endoscopy capacity is established.

Apparently lagging behind many Western countries in programme implementation, Norway has been in the frontline with regard to research on colorectal cancer screening. Three designs have been dominant: 1) randomized trials with pragmatic design to mimic “real-world” screening, i.e. invitation directly from the population registry without prior consent; 2) add-on sub-studies to improve services not only for screening, but also in routine clinics; 3) lifestyle surveys to explore the potential for primary preventive measures in connection with screening attendance, using this window of opportunity to more than screening, which is defined as a secondary preventive measure.

THE TELEMAR POLYP STUDY (TPS)

TPS in 1983 was the first ever randomized trial on endoscopy screening for CRC. It was a small-scale trial with 800 individuals aged 50-59 years, randomized 1:1 to sigmoidoscopy screening or no screening with a primary intention to test the feasibility of population screening by the use of endoscopy. The attendance rate

was an overwhelming 81% [5,6]. This was about the same time as another Norwegian small-scale non-randomized study obtained 55% attendance for screening using a guaiac-based fecal occult blood test (gFOBT) [7]. Secondary aims in TPS were to explore the epidemiology of rectosigmoidal polyps in an average risk population and to see if the prevalence and distribution of polyps in the population were comparable to findings in Norwegian autopsy studies [8,9]. The screening setting also facilitated a blinded study on polyp findings related to lifestyle, which included recording of body weight and measurement of dietary intake for five days before the endoscopic findings were revealed to the participant. These studies showed for the first time an association between colorectal polyps and smoking [10], a possible protective effect of cruciferous vegetables [11] and an association between the quality of drinking water and colorectal polyps [12]. Also for the first time, polyps <5 mm were left in situ to study changes in size and total polyp mass after two years in relation to lifestyle [13,14]. TPS also raised some concern that screening may have an unwanted effect on the motivation of polyp-free individuals to stick to a healthy lifestyle [15].

THE NORWEGIAN COLORECTAL CANCER PREVENTION TRIAL (NORCCAP)

The NORCCAP trial was a full-scale version of TPS with 21,000 individuals randomized to the intervention group and 79,000 to the control group – this time for the age groups 50-64 years with once-only sigmoidoscopy screening completed during the three-year period 1999-2001. With a 65% attendance and 10 years of follow-up, the cumulative CRC incidence and mortality rates were reduced by 20% and 27%, respectively [16]. Lifestyle changes through 3 years post-screening were less favourable in the screening than the control group [17], still remaining 11 years after sigmoidoscopy [18]. This suggested that a “health certificate effect” of normal findings at screening may reduce a motivation for maintenance of a healthy lifestyle or adjustments. This suggested a need for lifestyle information and advice within screening programmes [17]. A quality assurance

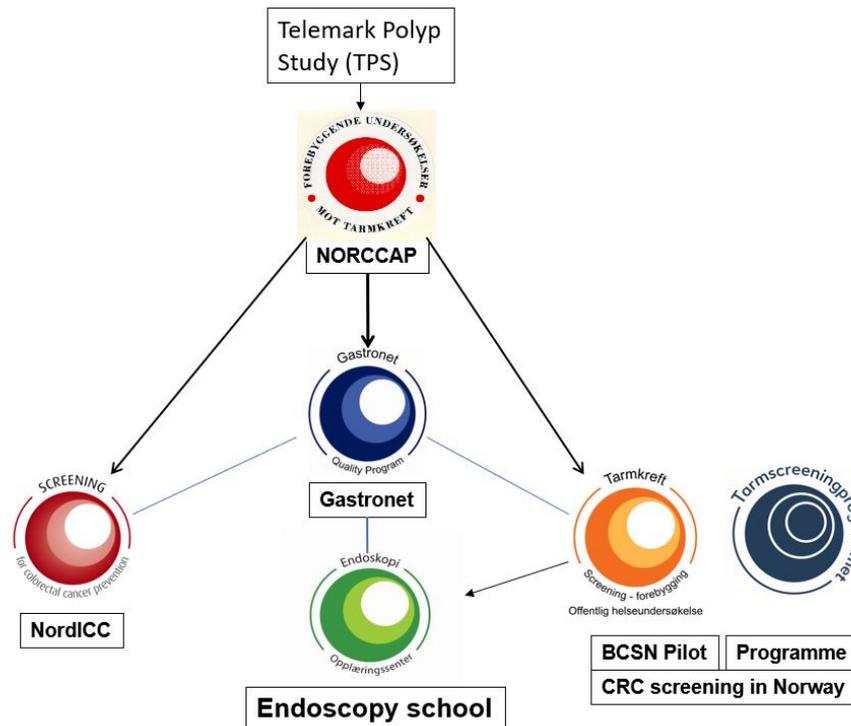


Figure 1. Colorectal cancer screening research in Norway. Interrelation of major screening research activities.

module for endoscopy within NORCCAP was launched as a stand-alone quality assurance programme for colonoscopy in the autumn of 2003 – named the Gastronet programme. At the same time, the Global Rating Scale (GRS) with their Joint Advisory Group (JAG) was introduced in the United Kingdom (<https://www.thejag.org.uk/>). Independently, these were the first two quality assurance programmes ever designed for colonoscopy.

Through NORCCAP, inter-endoscopist performance differences were published for the first time [19]. This led to establishment of the Norwegian Endoscopy School in 2011 (<https://endoskopiskolen.no/>). Based on Gastronet data, courses in the Endoscopy School have been shown to improve polyp detection rates and reduce pain experienced by women [20].

The large bowel has to be inflated somewhat during colonoscopy to visualize the bowel mucosa. NORCCAP research demonstrated benefits of CO₂ gas insufflation rather than using standard air. This was instrumental for the EU Commission Guidelines in 2010 recommending CO₂ insufflation during colonoscopy [21]. A major benefit of CO₂ insufflation is reduced pain and discomfort after the examination. In contrast to air, CO₂ is quickly absorbed through the bowel wall and exhaled through the lungs.

THE NORDIC INITIATIVE ON COLORECTAL CANCER (NORDICC)

After 5 years with futile attempts to raise funding for a large-scale randomized trial on colonoscopy screening in Norway (the NORCCAP-II trial), we established the

Nordic Initiative on Colorectal Cancer (NordICC) aiming for the same goal on an international level. When 1 million Euro was granted from each of the health ministries in Poland and the Netherlands, we succeeded in Norway. Sweden followed suit and the NordICC trial started in 2009. Primary results have not emerged yet [22].

BOWEL CANCER SCREENING IN NORWAY (BCSN)

NORCCAP was the first pilot of a possible national CRC screening programme in Norway, BCSN is the second pilot study – not to be confused with the national screening programme itself. BCSN is also a large-scale population screening study with a pragmatic design randomizing 140,000 men and women aged 50-74 years 1:1 to once-only flexible sigmoidoscopy or biennial FIT screening [23.] The study started in 2012 and is not yet completed, but important results have emerged. Possible unwanted lifestyle and psychological effects from screening suggested in the NORCCAP trial could not be seen in BCSN [24,25]. In BCSN, we explored the potential of using screening as a “teachable moment” for various ways of promoting healthy lifestyle [26]. This remains a major issue and will be pursued further in a large, randomized study to be launched within the national screening programme.

THE CRC BIOME STUDY

This is an ambitious study taking advantage of faeces biobank material stored for about 20 years since

screening in the NORCCAP trial and since 2012 in the BCSN trial [27,28]. The primary aim is to develop new screening modalities based on microbiota molecular profiles. The study will also explore interactions between lifestyle, dietary habits, microbiota and risk of CRC.

THE NORWEGIAN COLORECTAL CANCER SCREENING PROGRAMME

The international evidence in favour of CRC screening was considered sufficient for the EU Commission to recommend it for member states in 2003 [4]. Since then, there has been further accumulation of evidence for screening by means of faecal occult blood testing and endoscopy [29-31].

The Norwegian CRC screening programme will start off gradually with FIT screening for 55-year old men and women in 2022. The intention is to gradually convert to countrywide primary colonoscopy screening, depending on endoscopy capacity. This conversion process will take some time and in this period there may be some overlap in provision of FIT and colonoscopy to allow real-time evaluation of the two methods, e.g. evaluation of attendance by screening method may depend on travelling distance to endoscopy centres.

WHAT HAVE WE LEARNED?

There is an understandable reluctance to make a screening programme more complicated by introducing a series of randomized trials within its framework. There is, however, no other option when all relevant screening

age groups are embraced by national screening programmes in most countries – given the requirement that development and renewals of these programmes shall be based on science. When new, promising screening modalities (e.g based on blood sampling or microbiota) emerge in the future, they need to be tested at some stage in a valid target screening population. When national screening programmes cover the entire target population, such testing has to be carried out within the national programmes. Unfortunately, CRC screening has so far been introduced without sufficient prior knowledge of the efficacy of the various screening modalities [32]. Worldwide, political decisions have overruled a need for scientific evidence based on randomized trials.

During 20 years of hesitancy to follow EU screening recommendations for the high-risk Norwegian population, more than 160 original scientific publications and 20 PhDs have emerged from the above-mentioned and other CRC screening-related projects in Norway – many of them of great importance for routine, non-screening health services. This is surprising in light of considerable difficulties in fundraising for necessary trials as shown above. There is, however, great hopes that the use of this 20-year window of opportunities for screening studies has facilitated a broad political understanding of the need to prolong this research activity into the era and the domain of a national CRC screening programme. If so, then the Norwegian hesitancy has successfully paved the way for continuous improvement of health services in general.

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