The Cancer Registry of Norway – “a ground for scientific harvesting”

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ABSTRACT
The Cancer Registry of Norway (CRN) has been important in registry-based research in Norway for decades. The use of CRN in combination with other population-based registries and health surveys have been the basis for numerous research projects, which has contributed to fill important knowledge gaps. Researchers at the Norwegian Institute of Public Health and CRN have a long tradition of using these data sources to address research questions of common interests such as e.g. the effect of life style and diet on cancer risk. CRN and the Medical Birth Registry of Norway have co-existed for a long period, making it possible to study cancer incidence and birth characteristics over generations. During the last decades, several new registries such as the Norwegian Prescription Database and the Norwegian Patient Registry have been established, providing opportunities for studying for example drug use and cancer risk and the influence of comorbidities on the development of cancer.

In the future, the CRN will be an even more valuable data source when also other population-based registries and health surveys have existed for longer time periods.

INTRODUCTION
In Norway, we have a unique situation with population-based national registries, health registries and large health surveys (Figure 1). Although several registries and surveys are included in Figure 1, these are only the most important/relevant registries and health surveys available in Norway. By using these data sources, we can achieve new knowledge of disease trajectories by consolidation of disease endpoints across somatic disciplines, examining joint effects of life conditions, health behaviours, biological markers and socioeconomic circumstances throughout the life-course. By linking registries and other data sources, facilitated by unique personal identity numbers (PIN) assigned to all persons living in Norway, we can utilise individual data to elucidate plausible disease mechanisms, evaluate changes in prognosis, and identify targets for prevention applicable for the entire Norwegian population.

The Cancer Registry of Norway (CRN) is one of the oldest comprehensive population-based registries with mandatory reporting. CRN was established in 1952 and has data regarded as close to complete from 1953 (1). Further, we have the Cause of Death Registry electronically available from 1951 (2), the Medical Birth Registry of Norway (MBRN) from 1967 (3) and the Norwegian Surveillance System for Communicable Diseases (MSIS) from 1975 (4). Recently, we also have the Norwegian Immunisation Registry (SYSVAK) from 1995 (5), the Norwegian Prescription Database (NorPD) from 2004 (6), the Norwegian Patient Registry (NPR) from 2008 (7), the Control and Payment of Health Reimbursement (CPHR) from 2006 (7) and the Norwegian Registry for Primary Health Care (NRPHC) from 2017 (7). In addition, we have different registries and databases administered by Statistics Norway that include data on e.g. socioeconomy (8). Thus, when combining data, the research possibilities have expanded further. Similar registries also exist in the other Nordic countries (9).

Norwegian Institute of Public Health (NIPH) and CRN cooperate on several projects both presently and in the past. These projects have contributed with new knowledge about topics of common interest, and in the following we will give a few examples.

EXAMPLES OF PROJECTS USING DATA FROM NIPH AND CRN

Linkages between health surveys and CRN

Metabolic syndrome and cancer

The medical term metabolic syndrome (MetS) was introduced to characterise the metabolic picture of patients at increased risk of cardiovascular diseases in the 1980s. Several MetS definitions have been used, including different levels of metabolic aberrations such as obesity, hyperglycaemia, dyslipidaemia, and hypertension. Cohorts from Austria, Norway and Sweden were pooled in 2006 in the Metabolic Syndrome and Cancer project (Me-Can project), with linkages of data from health surveys (from 1972-2014) and cancer registries, including data from almost 600,000 men and women (10-12). The dataset has been used to study associations between various MetS factors and cancer risk. The Me-Can collaboration continued within Me-Can 2.0 (established in 2017) including researchers from CRN, University of Bergen (UiB) and NIPH. So
far, Me-Can has resulted in more than 30 scientific publications.

Me-Can has demonstrated that the MetS is positively related to risk of cancer, specifically to cancer of the liver, colorectum, endometrium, cervix, pancreas (women), and bladder (men), after adjusting for confounding factors such as smoking habits. Me-Can has also indicated that abnormal glucose metabolism is associated with increased risk of cancer overall and of several cancer sites, independent of body mass index (BMI), and has shown a small increased cancer risk in men with elevated blood pressure level.

Me-Can 2.0 data has shown that BMI is negatively related to breast cancer risk among premenopausal women, and that the association remained negative for years after menopause, although gradually waning by age (13). The association became positive only above the age of 62. It was also demonstrated that the TyG index (a surrogate measure of insulin resistance) significantly mediated the effect of overweight and obesity on risk of cancers of the pancreas, rectum, colon, kidney, and liver (14). In contrast, little or no mediation was observed for cancers of the endometrium, ovary and breast (women). Individual data from participants in several health surveys, giving longitudinal information, enabled us to study the impact of weight changes and timing of obesity on cancer risk (15). For example, being overweight before age 40 increased the risk of all obesity-related cancers by 15%, with higher risks particularly for endometrial, male renal cell and male colon cancer.

The combination of data from large health surveys and high-quality population-based cancer registries in three countries, including Norway, has been invaluable in Me-Can, making it possible also to study the risk of rare cancers.

Lifestyle, diet and cancer
It is well known that cigarette smoking and other lifestyle factors can increase the risk of cancer. Regional health surveys include questions about smoking habits, diet, physical activity at work and in leisure time, as well as measured body weight, blood pressure and blood lipids (16). By linking health survey data to the CRN, Cause of Death registry, Statistics Norway and the National Population Register, researchers have been able to relate lifestyle and living habits to the risk of various cancers taking socioeconomic status into account. Smokers are found to have a higher risk of breast cancer (17), colorectal cancer (18) and ovarian cancer (19). Laake et al. found that intake of trans fatty acids from partially hydrogenated fish oils was associated with increased cancer risk (20), whereas Emaus et al. found that prediagnostic measurements of BMI, blood pressure, serum lipids and physical activity were related to breast cancer prognosis (21). High alcohol consumption is found to increase the risk of several cancers. Tverdal et al., for instance, reported a positive association between alcohol consumption and colorectal cancer (22). Norwegians have a high consumption of coffee. An increase or decrease in cancer risk by coffee consumption could have an important impact on public health. A study by Tverdal supported the hypothesis of a lower risk of prostate cancer for heavy drinkers of boiled coffee (23). Another study did not support an inverse relationship between coffee intake and inci-
idence of cancer of the mouth or oesophagus, although a weak inverse relationship could not be excluded (24).

In 2018, an interesting follow-up of the Oslo Study Diet and Antismoking Trial was published. The study conducted in 1972/73 included men aged 40–50 years at high risk of coronary heart disease. Previous follow-up has shown that the intervention group had reduced cardiovascular events and mortality through 40 years. By linkage to CRN, the authors could demonstrate that the counselling also reduced the risk of cancer in overweight/obese subjects and smokers in the first 25 years of follow-up, but not in the long run (25).

**Links between NorPD and CRN**

**Drug use and cancer risk**

NorPD and CRN were linked to identify associations between use of prescription drugs and various types of cancer, for cancers diagnosed 2007-15 (26). In a nested case–control study associations between use of any prescription drug and risk for the 15 most common cancer types were assessed (27). This study confirmed previously reported associations, but the most important contribution was development of a tool for generating new hypotheses. An easy-to-use interactive online tool to display modifiable figures and tables was also developed (28).

**Improving prognosis of patients with glioblastoma: Linking health registry and clinical data to basic brain tumour research (GlioLink)**

Glioblastoma (GBM) is one of the deadliest human cancer types. The poor survival rates (median survival time less than 15 months) have, unlike many other cancers, not improved much during the latest decades. It has been indicated that some antipsychotics and antidepressants may influence the risk of GBM and the survival of GBM-patients.

The project GlioLink, led by the University of Bergen, combines basic brain tumour research with data from population-based health registries and clinical data, in order to screen brain penetrating drugs for their anti-tumour effects, to identify potential novel targets and develop new treatment strategies for GBM. The risk of GBM and the prognosis of GBM patients in relation to use of antipsychotics and antidepressants will be explored using Norwegian registries and databases, including CRN and NorPD. The results from the study will also be included in an international collaborative project.

**Long-term adverse health effects in cancer patients: Prescribing drugs in survivors of adult-onset cancer**

This project aims to examine the use of prescribed drugs, as proxies for specific diseases, in cancer survivors. Cancer survivors are compared with the general population by using nationwide registries, including CRN and NorPD.

Studies on drug use in survivors of colorectal and prostate cancer have been published (29,30). The prevalence of several drugs was higher in CRC-survivors than in the cancer-free population ten years after diagnosis, especially drugs for gastric acid disorder and pain medications (29). Among non-metastatic prostate cancer patients hormonal treatment was associated with an increased risk of cardiovascular disease (CVD) events, especially in patients with some CVD risk factors present at the time of their diagnosis and longer duration of treatment (30). We also found higher all-cause mortality among patients receiving hormonal therapy. We will also examine the drug use in survivors of gynaecologic, breast and thyroid cancers.

**Linkage of several data sources**

Cardiovascular disease, chronic lung disease, type 2 diabetes and cancer are the main non-communicable diseases (NCDs). They account for a major share of disease burden in Norway and other high-income countries. Further, mental health has become part of the NCD concept, and it is included in the sustainable development health goal of the United Nations by 2030. An ongoing research project, *A life-course approach to prevent non-communicable diseases (NCDs) in an ageing population – NCDNOR*, funded by the Research Council of Norway, utilises the unique research possibilities in Norway by compiling data from several registries and population-based health surveys. The project is based on a national collaboration launched in 2016 by the establishment of the Norwegian NCD indicator group, which also include users and stakeholders (31). The group was established for monitoring and prevention of NCDs based on the aim of the World Health Organisation (WHO) – to reduce premature mortality from NCDs by 25 percent between 2010 and 2025. WHO launched nine targets described as the “NCD targets” including 25 NCD indicators. The broad national research collaboration across institutions, including CRN, has been central in the development of NCDNOR.

The main objective of NCDNOR is to generate knowledge and identify plausible targets for prevention of NCDs by using a concept that includes consolidation of NCD endpoints across somatic disciplines, examining joint and interaction effects of socioeconomic circumstances, life conditions, health behaviours, biological markers and mental health throughout the life-course.

Previous studies examining associations between life conditions and health behaviours on health outcomes emerging later in life have largely relied on a ‘one-exposure, at one-time point’ approach. However, longitudinal population-based data is needed to study the occurrence and co-occurrence of NCDs and clustering of risk factors. Also, population-based studies of trends and patterns in multimorbidity and polypharmacy of NCDs in relation to socioeconomic status are limited, and longitudinal data on multimorbidity of NCDs including mental health are scarce. A recent report from
CRN showed large variation in cancer risk across educational levels, with patterns similar to those for other NCDs (32). Further, survival of cancer has improved, and in 2021, more than 316,000 persons were alive after a cancer diagnosis (1). The risk for other NCDs in the increasing number of cancer survivors is unknown. There are significant differences in the incidence between counties for several obesity- and smoking-related cancer types (32). However, these differences correspond to the incidence of other NCDs need to be revealed.

The utilisation of high-quality Norwegian registries and population-based health surveys as in NCDNOR has large potential to address research questions and provide new insight into topics that cannot be examined in randomised trials.

**Future perspective**

In the future, CRN will be an even more important data source for health research. Some of the shortcomings in Norwegian registry-based epidemiology have so far been that the NPR was not connected to the PIN before 2008. Further, International Classification of diseases (ICD)/International Classification of Primary Care (ICPC)-codes, giving codes for reimbursement, were not introduced in NorPD until March 2008. Medical information from the primary health care has, to some extent, been available in CPRH since 2006, but is more complete since 2017 when NRPHC was established. CRN has existed for 70 years and can now be used to examine cancer incidence over generations with possibilities for exploring patterns of comorbidity. Longer co-existence of the different registries will improve studies based on linkages between CRN, other registries and health surveys, for example studying the relation between maternal drug exposure before and during pregnancy and subsequent risk of childhood cancer. Increasing number of years with overlapping data form CRN, MBRN, NPR, NRPHC and NorPD will also improve the possibilities of performing studies on multimorbidity across somatic disciplines. We can also clarify the association between different cancers and other NCDs and elucidate disease patterns among cancer survivors. The access to linkable, individual-level data from different registries and population-based health surveys has been followed by an increased use of Norwegian data for research. Although MSIS and SYSVAK have not yet been broadly used in register-based epidemiologic health research projects, a utilisation of these registries linked to other health registries will expand our possibilities further by e.g., identifying plausible health effects of the recent COVID-19 pandemic, including vaccine effects. Thus, real world data based on linkages between nationwide health registers and health surveys will capture a wide range of research areas and become even more important in the future.

**References**


