



How can precision prevention be approached from a general population perspective within the field of cancer epidemiology?

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Precision medicine has been facilitated by increased data availability on patients, including biomarkers at the molecular level and comprehensive information from clinical investigations, while developments in big data analysis have helped generate insights from such extensive data. Sweden's innovation agency Vinnova has recently launched a widened area for research, development and innovation: *sustainable precision health* [1]. Sustainable precision health is about creating more accurate and precise methods for use in preventing, diagnosing and treating adverse health conditions, such as cancer, and promoting health and well-being.

Big data analyses in cancer research have mainly addressed precision medicine, aiming at improving diagnostics and prognostics in order to come up with more individualised and efficient treatments for cancer patients. Precision cancer prevention integration has emerged as a research concept for approaching individualised screening; early detection innovations have moved towards the integration of molecular knowledge and risk stratification profiles to allow for a more reliable representation of at-risk individuals [2]. In a commentary published in 2017, Paolo Vineis and Christopher Wild state that the 'precision' in precision prevention should refer to the individuals who are the targets of the intervention [3]. They also emphasise that without careful consideration being given to equitable access, more sophisticated medical interventions for prevention (or treatment) pose the unintended risk of exacerbating social inequalities in health, rather than reducing them [3].

Herein, I put focus on precision prevention from a general population perspective. I distinguish clinical cancer epidemiology from cancer epidemiology with a public health focus. The above-mentioned references to precision prevention connect to *clinical* cancer epidemiology; that is, a research field where precision prevention/medicine is approached by using epidemiological tools to study questions related to diagnosis, prognosis and treatment in clinical settings. Undoubtedly, big data analyses have been, and will be, of crucial importance for precision prevention/medicine relating to clinical care. In this Letter, however, I consider cancer epidemiology with a public health focus, which addresses questions relating to the cancer burden in the general

population. I take the view that cancer epidemiology addresses cancer in populations, rather than in individuals or patients [4]. Cancer epidemiologists build their studies on various types of data, not only comprehensive biomedical data but also data about lifestyle, environmental exposures, what people consume, where people live, how people move, which people participate in screening programs, etc. In public health research, precision prevention has been put forward as a concept that accounts for the social determinants of people's health, with interventions based on relevant lifestyle and environmental factors [5]. Usage of data on individuals of a general population is regulated by data protection and privacy laws. Investigators may collect individual data from population-based research studies with voluntary participation. However, extensive data on vulnerable individuals may be particularly hard to collect in population-based research studies. Follow-ups of the general population have revealed higher cancer incidences and mortality among non-participants compared to participants in population-based cohort studies [6]. Data may be accessible from population registers, including also information on non-participants. However, registry data on typical non-participants may be too sensitive, or too limited, for implementing individually tailored interventions in the general population.

The purpose of this Letter is to suggest a strategy of precision prevention that may help to make cancer prevention in the general population more efficient and describe how cancer epidemiology can contribute to this strategy.

Precision prevention by means of geographically targeted and contextualised interventions

It may be helpful to widen the focus of precision prevention to not only the smart use of data to build knowledge about *individual* conditions, but also to the use of neighbourhood-level data to build knowledge about *contextual* conditions [7, 8]. Geographical targeting on the small-area scale and adaptation to neighbourhood contexts could be means to obtain well-targeted and carefully adapted preventive interventions for a general population. Such interventions may be regarded 'precise' in the sense that they accurately target

population groups with heavier burden of cancer. This strategy of precision prevention may be viewed as a refined addition to the traditional population strategy of prevention, which seeks to control the determinants of cancer incidence in the population as a whole [9]. In a sense, it takes the population strategy closer to the 'high-risk' strategy of prevention, which seeks to identify high-risk susceptible individuals and to offer them some suitable protection [9].

Both higher incidences and later detection of tumours worsen the burden of cancer. It is therefore important that cancer incidence studies in the general population address not only cancer-specific incidences, but also incidences *per tumour stage at diagnosis*. If the stage dependent incidences are disregarded, the epidemiological basis for targeting of population groups with heavier burden of cancer will probably be incomprehensive. Furthermore, analyses of geographical and sociodemographic incidence variations in the general population should not be restricted to stratifications by a few regions and individual-level sociodemographic variables; incidence variations across small areas (neighbourhoods) and influence of contextual variables need to be analysed to facilitate the suggested strategy of precision prevention.

For example, let us consider the potential of epidemiological analyses to provide results that can help to design a precisely targeted and contextualised intervention aimed at increasing participation in organised screening for colorectal cancer. Such an intervention may be geographically target based on Cancer Stage Mapping, i.e. an analytic approach to revealing geographical differences in the burden of cancer on a small area scale [10]. Preferably, the small areas (neighbourhoods) should be defined with regard to socioeconomic conditions, segregation and population size [11, 12]. I reiterate that it is important that incidences per tumour stage at diagnosis are mapped separately because stage dependent incidences contribute differently to the burden of cancer. Colorectal cancer screening reduces the burden of colorectal cancer by shifting the incidence pattern towards earlier stage incidences [13] and by lowering the all-stage incidence in a long-term perspective [14, 15]. Whereas Cancer Stage Mapping helps to target the intervention, additional epidemiological analyses of screening uptake can help to adapt the intervention based on relevant neighbourhood-level/contextual variables. Inequalities in screening attendance across sociodemographic characteristics and neighbourhood contexts can be revealed by analysing geographical variations of screening uptake on a small-area scale [16]. Smart use of data to build knowledge about contextual conditions which associate with non-participation in cancer screening will be a key issue for success. The uptake of colorectal cancer associates with sociodemographic variables; socioeconomic and ethnic inequities in screening participation have been reported from studies in several countries [17–19]. Common indicators of neighbourhood deprivation, reflecting income level, educational level, unemployment and types of housing, as well as the distribution of immigrant groups, should therefore be considered [12, 20]. There are several other neighbourhood-level/contextual variables of potential interest:

population density, housing overcrowding, population turnover (people moving in and out in each year), daily movement statistics, access to recreation areas, access to health care, average travel time to screening clinic, etc. The intervention may, for example, consist of a modified invitation method, an educational campaign and/or a new organisation for decentralised screening (*cf.* [21–24]).

Generally, geographically targeted and contextualised interventions can be created and implemented based on neighbourhood-level data, including several contextual variables, basic demographics, number of cases diagnosed per tumour stage and, if a cancer screening programme has been implemented, number of persons screened. These types of interventions may not only be considered for making secondary prevention of cancer (early detection) more efficient, as exemplified above, but also for primary prevention and health promotion, with the ultimate goal to reduce the burden of cancer, especially in vulnerable population groups.

To sum up, from a public health perspective, sustainable precision health is a promising way forward to reduce the burden of cancer and promote health and well-being. Epidemiological analyses considering the general population can provide useful results for designing geographically targeted and contextualised interventions. The effectiveness of such an intervention need to be evaluated in a scientifically-sound way. Community intervention trials, comparing outcomes between carefully selected intervention and control neighbourhoods, will likely be essential for developing evidence. It should be acknowledged that such trails may be demanding and challenging. Experienced researches have stressed that consideration of governance, cost and research network support at the design stage of pragmatic trials of any community-based complex intervention is paramount [25]. Nevertheless, there is an urgent need for such trials. A recent Cancer Stage Mapping of colorectal cancer for the whole of Sweden showed that 208 out of 5984 neighbourhoods (small areas) had high burdens of this disease in the period 2015–2019, with evidently elevated incidences of advanced staged colorectal cancer in the age span 60–74 years as well as an elevated all-stage incidence in the extended age span 60–79 years [26]. It should be pointed out that Bayesian smoothing of the 5984 small-area standardised incidence ratios (SIRs) was applied. The corresponding posterior probabilities of $SIR > 1$ were considered for identifying the 208 neighbourhoods with an elevated burden of colorectal cancer, taking into consideration statistical aspects (e.g. optimising the balance between false-negatives and false-positives) [27]. These Cancer Stage Mapping results preceded the 19 regional programs for organised colorectal cancer screening that have now begun to be implemented for the age group 60–74. The other two of the 21 Swedish regions, Stockholm and Gotland, already had long-running organised screening programmes. The identified 208 neighbourhoods with high burdens of colorectal cancer, predominantly located in eight regions, were overrepresented in poorer neighbourhoods [26], where participation in screening programmes would be a concern in general. Furthermore, a

detailed comparison of the stage-specific incidences between Stockholm-Gotland and the other regions (corresponding to the intervention vs. control in this 'natural experiment' that has been ongoing since Stockholm and Gotland started running their programmes in 2008/2009) showed clear beneficial effects of the organised colorectal cancer screening in Stockholm and Gotland, which has resulted in both lower advanced stage incidences and a lower all-stage incidence in the 60-to-79-year-old age groups [26]. I conclude with a rhetorical question: Wouldn't it be a great opportunity for some of the regions in Sweden to achieve a potential gain by conducting geographically targeted and contextualised intervention trials aimed at optimising and equalising the uptake of colorectal cancer screening?

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