EPIDEMIOLOGY

Cancer survival: global variation and long-term trends

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Two recently published studies provide state-of-the-art evidence on the varying pace of improvement in survival across different cancers, and on inequalities in cancer survival between countries and regions. These studies offer rich and contrasting data that can guide policy priorities and research initiatives, and showcase the need for further development of population-based cancer surveillance across the globe.

The end of 2014 saw the publication of two important studies of cancer survival in large, geographically defined populations across different study periods.[1,2] They reveal variable improvements in cancer diagnosis and treatment, and provide insights into clinical, policy and research priorities.

In the first of these studies, CONCORD-2,[1] Allemani and colleagues analysed data from almost 26 million patients who were diagnosed with cancer between 1995 and 2009 in 67 countries or regions across the five continents, and reported survival outcomes for 11 cancer types: breast (in women), cervical, colon, liver, lung, ovarian, prostate, rectal, and stomach cancers in adults; and leukaemia, considered separately for adults and children. The outcome of the large-scale CONCORD Working Group Collaboration, this study sets a new standard for international comparisons of cancer survival, substantially exceeding the sample sizes, study periods, and geographical coverage of previous research efforts in this field.[3–5] Although data availability varied between registries, great care was taken in obviating ubiquitous challenges facing international studies of this kind—such as variations in classification and registration processes—using strict quality-assurance protocols.[1]

The CONCORD-2 investigators identified large-scale global inequalities in cancer survival for all of the studied cancers.[1] Although such correlations were not formally examined, between-country inequalities seem to broadly mirror disparities in human-development indices, with worse survival observed in patients in the least developed countries or regions.[1] Notable between-country variation was also apparent for cancers for which good survival outcomes are, in principle, achievable for most patients.[1] For example, for women diagnosed with breast cancer between 2005 and 2009, net 5-year survival exceeded 80% in most developed countries, but was probably lower than 60% in Algeria, South Africa, Mongolia, and Jordan.[1] Considering the overall number of potentially avoidable years of life lost, a disturbing picture also emerges for children diagnosed with leukaemia, with net 5-year survival estimates in recent eras of about 90% in central and northern Europe and North America, and lower than 65% in regions of China, Indonesia, Thailand, and Colombia.[1]

These comparisons are highly indicative of variation in the adequacy of early detection policies and the effectiveness of the health-care sector in different countries; however, they also signal the potential for global improvement. Indeed, it is probable that the steeper the survival gradients between countries, the greater the potential for relatively rapid improvement. These considerations, together with evidence on cancer incidence and mortality in relevant populations, can inform prioritization by policy makers and clinical leaders. Additionally, the CONCORD-2 findings underscore the need for the global development of cancer registration, a precious and scarce public-health tool. The great majority of future patients with cancer will be residents of countries or regions that are currently bereft of functioning cancer-registration systems.

In the second study, using data from more than 7 million patients from England and Wales, Quaresma and colleagues[2] estimated 40-year (1971–2011) trends in survival outcomes for 21 distinct cancer diagnosis categories: bladder, brain, breast (in women), cervical, colon, laryngeal, lung, oesophageal, ovarian, prostate, rectal, renal, stomach, testicular and uterine cancers, Hodgkin and non-Hodgkin lymphoma, leukaemia, melanoma, multiple myeloma, and 'other cancers'. Although previous studies have examined time trends in patient survival for various cancers in national (UK)

and subnational (US) populations,[6,7] this study extends such inquiries to a period of four decades. Importantly, the study also introduced a new composite measure, the index of cancer survival, which allows for summative ('all-cancer') evaluation of population trends in survival. This measure takes into account changes over time in patients' age and sex, and the incidence of cancers with differential prognosis.[2] Adaptation and application of similar approaches in future studies examining time trends in cancer survival in different countries and time periods would be useful.

The findings of Quaresma *et al.*[2] indicate a large average improvement in cancer survival over time, but with trends that vary widely by cancer site. Poignantly, for patients diagnosed in 2010–2011, net 10-year survival estimates ranged from 1% for pancreatic cancer to 98% for testicular cancer.[2]

Specifically, the authors report substantial improvements in 'all-cancer' survival between 1971 and 2011, with respective 1-year, 5-year and 10-year survival index estimates of 50%, 30% and 24% for English patients diagnosed in 1971, and 70%, 54% and 50% for those diagnosed in 2011.[2] Revealingly, cancer-specific trends indicate large variation in the pace of improvement by cancer type. Attention is drawn to three 'clusters' of cancers, characterized by both different survival outcomes and variable patterns of improvement.[2] For neoplasms such as breast, endometrial, and testicular cancers, melanoma, and Hodgkin lymphoma, sustained improvements in diagnosis and management have resulted in net 5-year survival of ≥80% for recently diagnosed patients.[2] At the other end of the spectrum lies a cluster of cancers, including brain, lung, oesophageal, pancreatic, and stomach cancers, for which 5-year survival remains ≤20%;[2] breakthroughs in diagnostic technologies to enable pre-symptomatic detection, and radically novel treatments are particularly needed for these malignancies.

Quaresma and colleagues[2] additionally examined how age inequalities in cancer survival have changed over time. Non-trivial differences in net survival between age groups were apparent for most cancers, but whether (and by how much) these 'age gaps' were narrowing or widening over time varied notably for different cancers.[2] The interpretation of these complex patterns is challenging without adjustment for probable biological differences between tumours at the same anatomical site in patients from different age groups, and without taking into account measures of morbidity and patient preference for different treatment options. Nevertheless, indirect comparisons with data from other European countries[8] might indicate cancers for which narrowing of age gaps in survival could be more easily attainable.

Both studies[1,2] estimated the survival of patients with cancer using 'net-survival' approaches to exclude causes of death other than cancer. Notable methodological innovations have recently occurred in survival analysis,[9,10] but critically, net-survival estimation requires accurate all-cause mortality information for reference populations stratified by age and sex, and, ideally, also according to other sociodemographic variables (such as race/ethnicity or socioeconomic status). These requirements can pose challenges both in terms of data availability and computation; for example, the CONCORD-2 investigators had to access or construct more than 6,500 different 'life tables' for respective populations and study eras as part of their analyses.[1]

Studying inequalities and time trends in cancer survival is critical for assessing progress in cancer control and informing research priorities. However, for the targeting of improvement efforts to be maximally effective, good-quality population-based data are also needed on variation in (often complex and variable) diagnostic pathways, and the use of various treatments (including the use of different modalities, delivered in combination or in sequence). Cancer survival can be considered a 'downstream' measure, which should ideally be interpreted together with intelligence on its 'upstream' determinants (Box 1). Therefore, even greater advances in public-health knowledge can be achieved by examining between-country or within-country variations in diagnosis, treatment, co-morbidities and health behaviours, together with survival outcomes. Despite the increasing availability of patient-level information from electronic health records and clinical audit or patient surveys, progress towards this ideal is impeded by (often exaggerated) concerns about the adequacy of anonymisation procedures, and (often overzealously interpreted) data protection regulations. It is impossible for doctors to treat patients effectively without information on their medical history; optimal decision-making about policy and improvement actions are similarly impossible without population-based evidence about the processes and outcomes of cancer care. The two recent studies[1,2] referred to herein should serve as poignant reminders of the need for continued and enhanced population-based cancer surveillance, endorsed by the public, health professionals, researchers,

legislators and politicians across the world.

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Box 1 | Understanding variation in cancer survival ~~between different populations and eras~~

Cancer ~~S~~stage at diagnosis and treatment factors (~~such~~access ~~to~~, and timeliness and comprehensiveness of therapies) are two important determinants of cancer survival ~~for individual patients;~~. ~~These complement the role oft~~ tumour biology and host factors (such as co-morbidity and frailty) ~~which~~ are related elements ~~also associated with~~influencing survival.

Variation in cancer survival between ~~different~~ populations ~~of patients~~ (or between patients of the same geographical population diagnosed in different eras) ~~is likely to~~might reflect variation in any of the~~se~~ ~~above~~ factors. If achievable, accurately apportioning such overall variations to their contributory factors ~~can~~could help to optimize cancer-control policies, ~~so that they are~~to enable them to be more ~~smartly~~rationally ~~directed~~ targeted ~~(targeted)~~ at the population or at different parts of the health-care system, and variably so for different cancers.

Unfortunately, deciphering ~~how much of~~to what extent variations in population survival reflect different ~~factors~~influences is challenging~~, as it requires~~, requiring information about a wide range of exposures ~~which~~that are rarely measured comprehensively in conventional cancer ~~registration~~registries, such as the following~~systems. These many include~~:

The availability and uptake of screening interventions (as applicable to different cancers)

The overall ~~length of intervals~~time from symptom onset to diagnosis of cancer (including both pre-presentation and post-presentation intervals)

Aspects of the health-care system that influence the speed of diagnosis (e.g. access to and availability of diagnostic services) and the delivery of 'state-of-the art' therapies

The distribution of psychosocial factors (~~such as~~ knowledge, attitudes and beliefs about cancer, and treatment preferences and expectations) in the population~~ these~~which in turn influence screening uptake, diagnostic intervals, and timeliness and comprehensiveness of treatment.

~~Likely a~~Artefactual influences (e.g. ~~because of~~ between-country or between-era differences in taxonomical definitions or surveillance system) ~~may~~ might also complicate interpretations.

Linkages of data from different sources can help to overcome some the difficulties in explaining variations in cancer survival between populations (or eras); however, ~~it is often the case that~~ data often need to be collected anew. This ~~is an evolving~~ research agenda is evolving, and is a challenge for population research on cancer, requiring multi-agency and multi-disciplinary collaborations within and between countries.