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Population-based cancer survival in the US: data, quality control and statistical methods

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Population-based cancer survival in the US: data, quality control and statistical methods

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Precis for use in the Table of Contents: Population-based cancer survival is a key measure of the overall effectiveness of health systems in managing the cancer burden. The high quality of US cancer registry data, 80% population coverage in the CONCORD-2 study and the use of an unbiased estimator of net survival ensure that the survival trends we report are robustly comparable by race and state. These results can be used to plan and evaluate cancer control strategy, in each state and for the US nationally.

Abstract

Background: Robust comparisons of population-based cancer survival estimates require tight adherence to study protocol, standardized quality control, appropriate life tables of background mortality, and centralized analysis. The CONCORD program established worldwide surveillance of population-based cancer survival in 2015, analyzing individual data on 26 million patients (10 million US patients) diagnosed 1995-2009 with one of 10 common malignancies.

Methods: In this *Supplement***,** we analyzed data from 37 state cancer registries covering approximately 80% of the U.S. population that participated in CONCORD-2. We performed data quality checks in three consecutive phases: protocol adherence, exclusions, and editorial checks. We estimated 1-, 3- and 5-year age-standardized net survival using the Pohar Perme estimator and state- and race-specific life tables of all-cause mortality for each year. We adopted the cohort approach for patients diagnosed 2001-2003 and the complete approach for patients diagnosed 2004-2009.

Results Articles in this *Supplement* report population coverage, data quality indicators and age-standardized 5-year net survival by state, race and stage at diagnosis. Examples of tables, bar-charts and funnel plots are provided in this article.

Conclusions Population-based cancer survival is a key measure of the overall effectiveness of services in providing equitable health care. The high quality of US cancer registry data, 80% population coverage and use of an unbiased net survival estimator ensure that the survival trends reported in this *Supplement* are robustly comparable by race and state. The results can be used by policy-makers to identify and address inequities in cancer survival, in each state and for the US nationally.

INTRODUCTION

Population-based cancer survival is a measure of the overall effectiveness of the health system in in dealing with cancer.[1] Comparisons of population-based cancer survival require adherence to a well-designed protocol, standardized quality-control procedures, appropriate life tables of background mortality and centralized analysis with the latest statistical methods.[2, 3]

CONCORD-2 established world-wide surveillance of cancer survival in 2015, with estimates of 5-year net survival based on individual data for more than 25 million cancer patients (about 10 million patients in the US) diagnosed during 1995-2009 with one of ten common cancers: stomach, colon, rectum, liver, lung, breast (female), cervix, ovary, prostate and leukemia in adults (15-99 years), and acute lymphoblastic leukemia in children (0-14 years).[3] Patients were followed up to Dec 31, 2009.

For the articles in this *Supplement*, we analyzed data from 37 statewide cancer registries (27 funded by the National Program for Cancer Registries (NPCR) program, 5 funded by the Surveillance, Epidemiology and End Results (SEER) program and 5 funded by both NPCR and SEER) that participated in CONCORD-2, covering approximately 80% of the U.S. population, and which agreed to the inclusion of their data in more detailed analyses by stage at diagnosis and by race. The CONCORD protocol required data on stage only for patients diagnosed from Jan 1, 2001, therefore these analyses, focused mainly on survival by stage, were restricted to patients diagnosed during 2001-2009.

Public health surveillance using the data from population-based cancer registries is a key component of cancer control.[4] The North American Association of Central Cancer Registries (NAACCR)[a] develops and promotes uniform data standards for all cancer registries in North America. Participating US registries had to meet the NAACCR certification criteria and to have conducted record linkage with both the state vital records and the National Death Index (NDI) to update the vital status of registered patients. NAACCR members developed a detailed SAS program to map the NAACCR database record structure to the CONCORD protocol and thus to enable all North American registries to exclude cases that would not have been considered reportable primaries according to the International Association of Cancer Registries (IACR) multiple primary rules,[5] before their datasets for 1995–2009 were extracted for CONCORD-2. This was necessary because North American registries define

[a] http://www.naaccr.org/standardsandregistryoperations/volumeii.aspx

multiple primary cancers under the rules of the Surveillance, Epidemiology and End Results (SEER) program,[6] whereas registries in the European Network of Cancer Registries (ENCR) and in other continents generally use the rules of the IACR,[5] which are more conservative.

Topography and morphology were coded according to the International Classification of Diseases for Oncology (3rd edition; ICD-O-3[7]). Solid tumors were defined by anatomical site (**Table 1**). For ovarian cancer, we included the fallopian tube, uterine ligaments, and adnexa, and the peritoneum and retroperitoneum, where high-grade serous ovarian carcinomas are often detected; this was done to improve international comparability of the data sets. Kaposi's sarcoma and solid tumors with lymphoma morphology were excluded from analysis.

Leukemias were defined by morphology. In this *Supplement* we cover only precursor-cell acute lymphoblastic leukemia in children (ICD-O-3 morphology codes 9727, 9728, 9729, 9835, 9836, 9837). Estimates of survival by race, state and sub-type of adult leukemia will be presented in other publications.

Only primary invasive cancers (ICD-O-3 behavior code 3) were included in survival analyses. We included cancers at a given site regardless of whether the patient had had a previous cancer. If a patient was diagnosed with two or more cancers of a given organ, including paired organs, during 2001-2009, only the first was considered in survival analyses.

Follow-up

US registries were asked to submit follow-up data (vital status and date of last known vital status) as at Dec 31, 2009, after conducting linkages of all cancer registrations with both state vital records systems and the NDI. Patients whose cancer registration could not be linked to a death record were considered to be alive on Dec 31, 2009 (passive follow-up, also known as the "presumed alive" method).

SEER registries are required to meet a specific standard for the completeness and recency of follow-up. At least 90% of registered patients not known to be deceased were required to have a date of last known vital status on or after Jan 1, 2010. These follow-up dates could have been obtained from either passive or active follow-up.[8]

Patients whose survival time was unknown were excluded from analyses. This group comprised patients registered solely from a death certificate or diagnosed at autopsy.

CONCORD-2 data quality control: three phases

We performed data quality checks in three consecutive phases: protocol adherence, exclusions, and editorial checks. After each phase a detailed report was sent to each cancer registry.

Phase 1: Protocol adherence

We first checked the compliance with the CONCORD-2 protocol of each of 37 variables (demographic characteristics, basis of diagnosis, date of diagnosis, topography, morphology, behavior, stage, vital status, date of last known vital status) in each tumor record in each data set. Any value not specified in the protocol was considered non-compliant. Each registry was sent a table of the number of records and the percentage compliance for each variable, and for each cancer. Minor issues were corrected by the CONCORD Central Analytic Team, after discussion with the registry. For major structural issues, 5 registries corrected and re-submitted their data.

Phase 2: Exclusions

Next, we checked for logical inconsistencies between the variables in each tumor record, for each cancer site. Exclusion criteria were defined *a priori,* based on the experience within the Cancer Survival Group, the checks performed in the first CONCORD study, the EUROCARE (EUROpean CAncer REgistry based study on survival and care of cancer patients) data quality checks, the checks proposed by the International Agency for Research on Cancer (IARC), the descriptions of morphology in the World Health Organization (WHO)/IARC Classification of Tumors for each cancer and, finally, clinical expertise.[3]

We produced "exclusion tables" summarizing the quality of each data set. Data quality indicators were tabulated separately for patients diagnosed in 1995-99, 2000-04 and 2005-09, to enable evaluation of trends in data quality over time. We defined three broad categories for exclusion: ineligible (e.g., *in situ* neoplasm), definite error (e.g., sex-site mismatch) and possible error (e.g., apparent inconsistency between site and morphology). We had requested records of *in situ* neoplasms to assess the intensity of diagnostic activity, particularly for cancers of the breast and cervix, but *in situ* neoplasms were not included in survival analyses. The number and percentage of patients excluded from analysis are shown in **Table 2**.

The majority (99.6%) of patients only had a single tumor record for any one cancer during 1995-2009. However, since a small proportion of patients had more than one tumor record for a given cancer ("multiple tumor, same site"), it was necessary to apply the quality control checks to every tumor record independently before selecting the single tumor record to be included in survival analyses. For example, if a woman had an *in situ* neoplasm of the breast diagnosed in 2001 followed by an invasive primary breast cancer in 2007, the invasive cancer record was selected for inclusion in the analyses, provided it was free of error.

Phase 3: Editorial tables

We evaluated the distribution of key data quality indicators for each cancer and for each registry. These indicators included the proportion of cancers in the final data set that had been microscopically verified and the proportion of patients who had been lost to follow-up. We also checked the distributions of the day and the month of the dates of birth, diagnosis and last known vital status. These distributions should be flat, since one would expect about 8% of births, diagnoses and deaths to occur in each month, and about 3% on each day of a given month, except days 28-31: spikes in these distributions, often on the 1st, 15th or 16th day of the month, or for June or July, help to identify where registries had imputed missing elements of each date.

Table 2 provides a summary of the exclusions and data quality indicators for adults (15-99 years) diagnosed during 1995-2009 with one of 9 common cancers (all solid cancers), by US state. The calendar periods within which survival analyses could be performed by stage at diagnosis were constrained by the availability of data on stage only from 2001, and the change in coding from 2004 (see below). Therefore, the periods for which data quality indicators are presented do not exactly match the periods used for survival analysis. However, data quality has generally been very high in all US registries, and it tended to improve over the 15 years from 1995 to 2009. Only about 2% of tumors were registered from a death certificate only (DCO) or detected solely at autopsy. These records must be excluded from survival analyses because the follow-up time for these patients is unknown. However, the proportion of DCO registrations in the US was low overall (1.9%) and in all states (range: <0.1-3.5%). The proportion of other errors was very low (0.2%). Therefore, about 98% of the eligible patients were included in survival analyses. Practically all tumors (99.7%) were microscopically verified: this proportion was over 95% in almost all US states.

The proportion of the US population covered by this study is 80.6%. **Table 3** shows the population coverage by US state, as well as the number of patients diagnosed during 1995–2009 and included in the analyses.

Study design

The focus of this monograph is on the striking differences in survival by race and stage at diagnosis. Since differences in survival between men and women were generally very small, compared to the differences in survival between blacks and whites (Table 4), we do not show survival estimates by sex in the articles on each cancer.

The CONCORD protocol required information on stage at diagnosis only for patients diagnosed from 2001 onward, because the completeness of data on stage in the US and many other countries was known to be much lower before 2001. For the analyses of survival by stage at diagnosis, patients were grouped by year of diagnosis into two calendar periods (2001-2003 and 2004-2009) to reflect changes in the methods used by US registries to collect data on stage at diagnosis. From 2001, most registries coded stage directly from the source data to SEER Summary Stage (SS) 2000.[9] From 2004, all registries began to derive Summary Stage 2000 from 15 pathological and clinical data items, using the Collaborative Staging System.[10] Data on stage at diagnosis were not available for Maryland or Wisconsin, or for cases diagnosed during 2004-2009 in Rhode Island.

We estimated net survival using the cohort approach for patients diagnosed in 2001-2003, since all patients had been followed up for at least five years by Dec 31, 2009. We used the complete approach to estimate net survival for patients diagnosed from 2004-2009, because five years of follow-up data were not available for all patients.

Cohort approach

The cohort approach is the classical approach to survival analysis, in which all patients who are included in the analyses have had the opportunity to be followed for the full duration of survival analysis, in this case, five years. The cohort of patients is defined by the year or calendar period during which they were diagnosed, and each patient is followed up for the same length of time. In our analyses, at least 5 years of follow-up for vital status were available by the end of 2009 for all patients diagnosed during 2001-2003. Each patient,

irrespective of their actual year of diagnosis, contributes survival information at each point in follow-up time that, taken cumulatively, make up the survival estimate at 5 years.

The cohort approach[11, 12] is considered the gold standard,[11, 12] because it provides a survival estimate for a group of patients who were diagnosed during the same year or period, who are likely to have been treated in similar fashion, and who have all been followed up for at least the duration of survival required. It is the natural approach to estimation of outcome, and is easy to interpret, but other approaches may be required if sufficient data are not available.

Complete approach

The complete approach can be applied to estimate survival for patients who were diagnosed more recently, and for whom 5 full years of follow-up data may not be available at the closing date of the study. For example, some patients diagnosed 2004-2009 were followed up for less than 5 years. The 'cohort' approach can be used to estimate five-year survival for patients diagnosed in 2004, but 5-year survival can be estimated for the whole calendar period with the 'complete' approach, in which all the available follow-up data for patients diagnosed during 2004-2009 are used. The potential follow-up time for these patients varies between 1 year and 5 years.

Age standardization

We compared survival estimates between US states, between blacks and whites, and between calendar periods of diagnosis. For age-specific survival estimates, comparison between populations or over time is straightforward, but if we want to compare overall (all-ages) survival estimates, age standardization is required. This is essentially for the same reasons as in comparison of overall incidence or mortality rates, namely that net survival may also vary widely with age at diagnosis, and the age profile of cancer patients may differ between the populations or change between the calendar periods among which we wish to compare overall survival.

For age-standardization of incidence or mortality rates, what matters is the age structure of the general population at risk of cancer. With cancer survival, however, what matters is the age profile of cancer patients, which is very different from the age profile of the general population. The weights used for age standardization of cancer survival estimates are thus completely different from those required for standardizing incidence or mortality rates. The

weight for each age group is provided by the proportion of cancer patients in that age group in a standard population of cancer patients.

The International Cancer Survival Standard (ICSS) weights[13] are strongly recommended for international comparisons of cancer survival. They comprise three sets of standard age weights, derived from discriminant analysis to find the smallest number of sets of weights that enable adequate standardization of survival. Each standard is applicable to a range of different cancers, and provides age-standardized survival estimates that are not too different from the unstandardized estimates. The same age weights can be used for men and women, and for direct comparisons of age-standardized net survival between patient groups defined by sex and race.

Statistical methods

We estimated net survival up to 5 years after diagnosis, with 95% confidence intervals (CI), using the Pohar Perme estimator,[14] implemented in the *Stata*[15] algorithm *stns*.[16] We analyzed survival by state, race, stage at diagnosis and calendar period of diagnosis. Net survival is the probability of surviving up to a given time since diagnosis after controlling for other causes of death (background mortality). To control for the wide differences in background mortality among participating states and racial/ethnic groups, we constructed life tables of all-cause mortality in the general population of each state from the number of deaths and the population, by single year of age, sex, calendar year and, where possible, by race (black, white).

Net survival in adults was estimated for five age groups (15-44, 45-54, 55-64, 65-74, and 75-99 years; except for prostate cancer 15–54, 55–64, 65–74, 75–84 and 85–99 years). We obtained age-standardized survival estimates using the International Cancer Survival Standard (ICSS) weights. For children, survival was estimated for the age groups 0–4, 5–9 and 10–14 years. We obtained age-standardized estimates by assigning equal weights to the three age-specific estimates.[17]

We derived standard errors for both unstandardized and age-standardized survival estimates using the Greenwood method,[18] assuming a normal distribution, and truncated to the range 0–100. We did not estimate survival if fewer than ten patients were available for analysis. Age-standardization was only performed if there were at least 10 patients in each of the age

categories specified above. If an age-specific estimate could not be obtained, we merged data for adjacent age groups and assigned the combined estimate to both age groups. If two or more age-specific estimates could not be obtained, we present only the pooled, unstandardized estimate for all ages combined: these estimates are italicized in Tables 2 and 3 of the Appendix.

For each of the 37 states, we present estimates of age-standardized net survival for each cancer up to 5 years after diagnosis. For convenience, we report cumulative survival probabilities (in the range 0-1) as percentages in the range 0-100%.

Life tables

For the analyses presented in this *Supplement*, we used the life tables for background mortality that were constructed for the CONCORD-2 study.[19]

To control for variation between US states in background mortality by age, sex, race and calendar year while estimating net survival, we used life tables of all-cause mortality rates by single year of age (0-99 years), for each state, race, calendar year (2001-2010) and sex. For a few states in which the black population is small, it was not possible to construct adequately robust life tables of all-cause mortality by single year of age and sex for blacks, so net survival estimates for blacks in those states are not presented separately. These life tables can be downloaded from the CONCORD library of over 12,000 life tables.[20] The library includes detailed statistical and graphical reports on the robustness of the life tables for each US state.

We received raw data on death counts and populations for each US state. To produce life tables for each US state by race, sex and calendar year (state- and race-specific life tables) we used a flexible Poisson model[21] that enables creation of single-year-of-age life tables even when the raw data are sparse. We checked the life tables by examination of semi-log plots of age-sex-mortality rates, life expectancy at birth, the probability of death in the age bands 15–59, 60–84 and 85–99 years and, where necessary, the model residuals, to examine the goodness of fit of the models by age and sex.

Graphical representation

In each cancer-specific article in this *Supplement*, trends, geographic variations and differences in age-standardized survival by race are presented graphically in bar-charts and funnel plots.[22]

Bar-charts

Results were summarized in bar-charts of 5-year age-standardized net survival by calendar period (2001-2003 and 2004-2009), for each state, grouped within the four US geographic Census Regions (Northeast, South, Midwest, West). The results for each Region are presented with a different color. Within each Region, darker shades indicate NPCR registries, while lighter shades indicate SEER registries. Five registries funded by both SEER and NPCR were grouped with SEER because they use both passive and active follow-up; they are indicated with an asterisk "*".

The survival estimates for each state in 2004-2009 are ranked from high to low within each US Census Region. The same ranking is then applied to the results for 2001-2003, to facilitate examination of changes in survival from 2001-2003 to 2004-2009 within each state. The absolute difference (%) in 5-year net survival between the two periods is also shown for each state.

Each graphic includes the pooled survival estimates for all 37 participating states combined.

Funnel plots

Funnel plots are graphical representations designed to detect excessive variation in performance indicators by simple visual inspection of the data.[23] They can be used to provide a simple and informative display of geographical variation or time trends in population-based cancer survival measures (e.g. age-standardized net survival).

A funnel plot comprises four elements:[22] the target (or reference) value for the outcome, a set of control limits (the funnel), data points for the outcome variable (indicator) and the associated precision parameter for each data point. Data points outside the control limits (the funnel) indicate variation in the indicator beyond what would be expected by chance, while taking account of precision.[23]

The funnel plot in Figure 1 shows, as an example, 5-year age-standardized net survival for breast cancer in the US during 2004-2009, by race and state. It is constructed by plotting the 37 state-specific survival estimates for breast cancer during 2004-2009, on the y-axis, against

their associated precision, on the x-axis, forming a scatter plot. Fewer data points are available for blacks (28 states) than for whites (37 states), because of the difficulty in constructing robust life tables for blacks in every state. The precision parameter in this example is in fact the precision of each age-standardized net survival estimate (the inverse of its variance). This is a natural choice to represent the statistical precision of each estimate, but it could be any function that is proportional to the inverse of the variance.

The target (the solid horizontal line in Figure 1) is then superimposed. This is a constant value, considered independent of the observations, and it specifies the expected value for the outcome. The target shown in Figure 1 is the 5-year age-standardized net survival estimate for the pooled US data for women diagnosed with breast cancer during 2004-2009. The pooled US estimate was selected as the target to show the extent to which survival for blacks and whites in each state varies around the overall survival estimate for the US.

The control limits (the dashed lines in Figure 1) are also independent of the individual survival estimates. They depend only on the target value, and their correct formulation depends on the underlying theoretical distribution of the target value. The control limits for a given level of significance (α) are drawn around the target value across the entire observed range of precision of the individual estimates. The most common levels of significance are α=5% and α=0.2%, so that the resulting 95% and 99.8% control limits represent approximately two and three standard deviations, respectively, on either side of the target value, at each level of precision. An estimate that appears outside the control limits is identified as diverging from the target value, and is an "out-of-control" estimate, in other words a probable outlier that may need to be investigated further.

In Figure 1, as with all the funnel plots reported in this *Supplement*, 5-year age-standardized net survival is represented by open circles for white patients and by solid circles for black patients. Funnel plots are extremely powerful tools for visual examination of variation in an indicator: we can perceive at first glance that 5-year survival in blacks is persistently lower than would be expected (the pooled US survival estimate, the "target") and that survival for blacks is generally lower than for whites.

DISCUSSION

This article summarizes the data quality control procedures, analytic methods and graphical presentations that have been deployed for all the data sets reported in this *Supplement*. The quality of population-based data from the 37 participating US cancer registries was impressively high (Table 2). More details about the quality indicators for each cancer can be found in the web-appendix[b] to the CONCORD-2 article.[3]

For NPCR registries that use only passive follow-up to determine the vital status of registered cancer patients (the "presumed alive" method), survival estimates may be inflated if the cancer registrations for some patients who have in fact died could not be successfully linked to the data from their death certificate. The vital statistics offices in each state have reported all death certificate information to the National Death Index (NDI) since 1979. Passive methods of follow-up are known to be efficient because of the completeness and accuracy of the National Death Index, which tends to capture 1-3% more deaths than if the registry can only link its data to the state death index[24]. Most of the extra deaths captured in this way will be those of patients who migrated to a different state following their cancer diagnosis. However, the registries included in these analyses had all matched their data against the National Death Index before data submission, so the completeness of vital status ascertainment is expected to be extremely high, although it may not capture out-of-country deaths.

A major strength of this study is the use of life tables that are specific for each state, each race (white, black) and each calendar year, to control for differences and changes in background mortality by single year of age, sex, race and single calendar year. This approach provided the tightest possible control of background mortality with the available data. More specific life tables may be considered in future studies, subject to the availability of high-quality data on death and population counts for Hispanics or other major racial or ethnic groups.

The CONCORD-2 protocol required registries to provide information on stage at diagnosis for patients diagnosed in 2001 or later. Calendar years of diagnosis were then grouped for analysis of survival by stage into 2001-2003 and 2004-2009, to reflect a change in the US stage coding system from 2004.

This choice of calendar periods imposed the following selection of analytic approach. We were able to estimate 5-year net survival with the cohort approach for patients diagnosed in 2001-2003, since all patients had at least 5 years of potential follow-up. However, the period

[b] http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(14)62038-9/supplemental

approach[25] that was adopted to estimate 5-year survival for patients diagnosed 2005-2009 in the CONCORD-2 study[3] could only have been used to estimate 5-year survival by stage for patients diagnosed during 2004-2009 if stage data had also been available for patients diagnosed in 2000. We therefore adopted the complete approach. In this approach, more information is available to estimate survival in the early years of follow-up than later years. Only patients diagnosed in 2004 had the potential to be followed up for 5 years by Dec 31, 2009; only patients diagnosed during 2004 and 2005 had the potential to contribute to the conditional survival probabilities between 4 and 5 years after diagnosis; and so on. This leads to some increased variation around the 5-year survival estimates for 2004-2009 compared with those for 2001-2003. This is reflected in the confidence intervals, and slightly lower precision, seen in the funnel plots for 2004-2009 in some of the site-specific articles.

This is the most extensive analysis of 5-year population-based cancer survival in the US to date, with survival trends for 10 common cancers in 37 states that include 80% of the US population. Here, we have focused on variations in survival by race and stage at diagnosis for patients diagnosed during 2001-2009.

Population-based cancer survival is a key measure of the overall effectiveness of the health system in in dealing with cancer. The high quality of the data from the US cancer registries, implementation of the most up-to-date and unbiased estimator of net survival, combined with the use of state- and race-specific life tables, all help to ensure that these cancer survival estimates are robust and comparable. We believe they can be confidently used by policy-makers to identify inequities in cancer survival by race in each state and for the US as a whole, and to plan cancer control strategies that promote equal opportunity for the best possible outcomes after a cancer diagnosis.

Legends for Tables and Figures

Table 1 Definition of malignancies

Table 2 Data quality indicators for patients diagnosed during 1995–2009, by US state (all solid cancers combined)

Table 2 footnotes:

[a] *In situ* malignancy (ICD-O-3 behavior code 2): some registries do not register in situ cancers; other registries did not submit them. Other: records with incomplete data, or for tumors that are benign (behavior code 0), of uncertain behavior (1), metastatic from another organ (6), or unknown if primary or metastatic (9); or for patients with age outside the range 15-99 years (adults).

[b] DCO: tumors registered from a death certificate only (DCO), or detected solely at autopsy. Other: vital status or sex unknown; invalid sequence of dates; inconsistency of sex-site, site-morphology, age-site, age-morphology, or age-site-morphology.

[c] MV: microscopically verified. Non-specific morphology (solid tumors only): ICD-O-3 morphology code in the range 8000-8005. Censored: patients diagnosed during 1995-2004, with last known vital status "alive", but less than five years of follow-up.

[d] P=Passive ("presumed alive") method; P&A=Passive and Active ("reported alive") methods; see text.

Table 3: Population coverage and number of patients diagnosed during 1995–2009, by US state

Table 3 footnotes:

[a] Data are from the UN Population Division for 2009

[b] Acute lymphoblastic leukemia, children (0-14 years) only

Table 4: Age-standardized 5-year net survival (NS, %) for adults (15-99 years) diagnosed with one of 10 common malignancies and children (0-14 years) diagnosed with acute lymphoblastic leukemia (ALL) during 2004-2009, by race and sex: United States[a]

Table 4 footnotes:

[a] Population coverage represents 80.6 % of the US population in 2009 (UN Population Division)

[b] A negative value means that males have lower survival than females

[c] A negative value means that blacks have lower survival than whites

[d] Acute lymphoblastic leukemia, children (0-14 years) only

Figure 1: 5-year age-standardized net survival for women (15-99 years) diagnosed with breast cancer in 2004-2009, by state and race

Figure 1 footnote: Each data point represents the survival estimate for a US state, either for blacks (28 states) or whites (37 states; see text).

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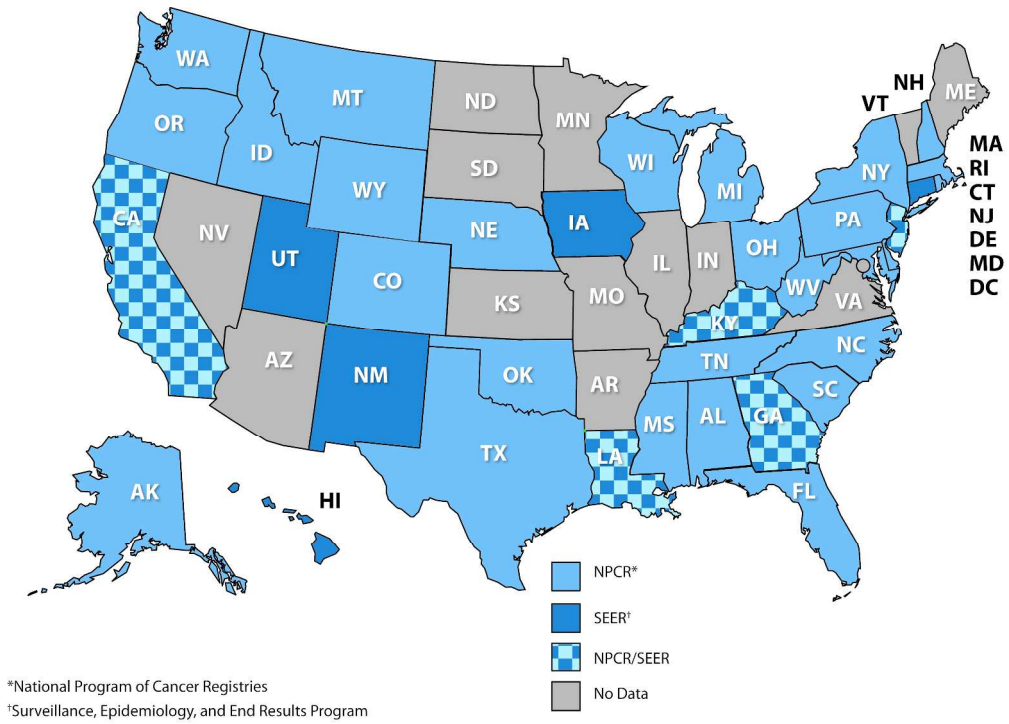

Figure 1

261x196mm (300 x 300 DPI)

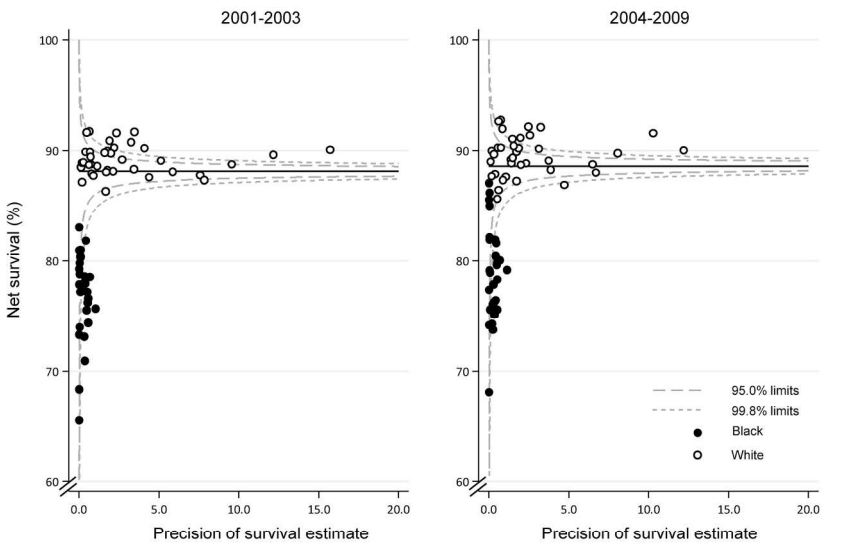

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Table 1 Definition of malignancies

Malignancy	Topography or morphology codes	Description
Stomach	C16.0-C16.6; C16.8-C16.9	Stomach
Colon	C18.0-C18.9; C19.9	Colon and rectosigmoid junction
Rectum	C20.9; C21.0-C21.2, C21.8	Rectum, anus and anal canal
Liver	C22.0-C22.1	Liver and intrahepatic bile ducts
Lung	C34.0-C34.3; C34.8-C34.9	Lung and bronchus
Breast (women)	C50.0-C50.6; C50.8-C50.9	Breast
Cervix	C53.0-C53.1; C53.8-C53.9	Cervix uteri
Ovary	C48.0-C48.2; C56.9; C57.0-C57.4; C57.7-C57.9	Ovary, fallopian tube and uterine ligaments, other and unspecified female genital organs, peritoneum and retroperitoneum
Prostate	C61.9	Prostate gland
Leukaemia (children)	9727; 9728; 9729; 9835; 9836; 9837	Precursor-cell acute lymphoblastic leukaemia (ALL)

			Ineligible (%)[a]			Exclusions (%)[b]			Data quality indicators (%)[c]				
	Calendar period	Patients submitted	In situ	Other	Eligible patients	DCO	Other	Available for analyses	MV	Non-specific morphology	Lost to follow-up	Censored	Type of follow up[d]
US registries	**1995 - 2009**	**10,115,271**	**6.4**	**1.4**	**9,325,815**	**1.9**	**0.2**	**9,142,718**	**99.7**	**1.3**	**1.0**	**<0.1**	
Alabama	1996 - 2009	184,581	0.0	1.3	182,156	1.9	0.2	**178,484**	95.9	1.1	0.0	0.0	P
Alaska	1996 - 2009	19,959	6.9	2.9	18,002	0.7	0.2	**17,852**	95.8	1.7	0.0	0.0	P
California	1995 - 2009	1,326,462	6.1	2.1	1,218,053	1.2	0.2	**1,202,096**	95.8	0.8	3.2	0.0	P & A
Colorado	1995 - 2009	162,405	6.4	1.4	149,860	2.4	0.2	**146,306**	95.8	0.8	0.0	0.0	P
Connecticut	1995 - 2009	180,154	7.8	1.1	164,128	1.3	0.2	**161,865**	97.0	0.7	4.5	0.0	P & A
Delaware	1995 - 2009	41,768	6.1	1.2	38,717	2.0	0.2	**37,956**	96.1	0.7	0.0	0.0	P
Florida	1995 - 2009	928,713	5.0	0.8	874,825	3.3	0.2	**846,156**	97.2	1.5	0.0	<0.1	P
Georgia	2000 - 2009	241,967	6.0	0.6	225,831	1.8	0.2	**221,675**	96.2	0.7	2.1	0.0	P & A
Hawaii	1995 - 2009	55,510	7.6	1.0	50,774	1.2	0.2	**50,116**	96.6	0.3	4.1	0.0	P & A
Idaho	1995 - 2009	51,319	4.6	1.3	48,277	2.5	0.2	**47,086**	95.8	0.4	0.0	0.0	P
Iowa	1995 - 2009	146,231	5.0	1.3	136,938	1.5	0.2	**134,776**	95.2	0.5	1.4	0.0	P
Kentucky	1995 - 2009	208,365	4.7	0.8	197,074	1.4	0.2	**194,119**	93.7	1.4	1.1	0.0	P & A
Louisiana	1995 - 2009	205,149	4.4	1.1	193,856	1.5	0.2	**190,693**	95.2	0.4	2.2	0.0	P & A
Maryland	1996 - 2009	225,540	10.6	1.1	199,088	2.9	0.3	**193,230**	94.8	1.8	0.0	0.0	P
Massachusetts	1995 - 2009	336,858	9.1	0.8	303,282	1.7	0.2	**297,992**	95.8	1.4	0.0	<0.1	P
Michigan	1995 - 2009	522,531	12.9	1.0	449,914	1.1	0.2	**444,382**	94.7	3.0	0.0	0.1	P & A
Mississippi	2003 - 2009	64,396	4.7	0.9	60,833	3.1	0.2	**58,974**	96.7	0.4	0.0	0.0	P
Montana	1995 - 2009	48,221	10.1	1.7	42,512	3.5	0.2	**41,087**	95.8	0.3	9.8	0.0	P & A
Nebraska	1995 - 2009	88,971	4.9	1.5	83,231	1.5	0.2	**81,980**	96.1	1.2	0.0	<0.1	P
New Hampshire	1995 - 2009	60,507	7.6	0.9	55,347	1.7	0.2	**54,345**	95.1	1.1	0.0	0.0	P
New Jersey	1995 - 2009	440,395	6.7	1.6	403,724	1.3	0.2	**398,191**	96.2	1.0	2.8	0.0	P & A
New Mexico	1995 - 2009	70,628	5.4	0.8	66,269	3.1	0.2	**64,241**	94.8	1.1	5.1	0.0	P & A
New York	1995 - 2009	940,361	7.7	2.6	842,888	1.7	0.2	**827,621**	94.8	0.9	0.0	0.0	P
North Carolina	1995 - 2009	375,205	5.9	0.7	350,656	1.7	0.1	**344,750**	96.3	0.7	0.0	0.0	P
Ohio	2001 - 2009	334,006	6.1	0.7	311,520	2.8	0.2	**303,146**	96.3	2.0	0.0	0.0	P
Oklahoma	1997 - 2009	147,158	4.3	1.0	139,322	2.9	0.2	**135,165**	93.1	1.6	0.0	0.0	P
Oregon	1996 - 2009	155,767	5.3	0.8	146,145	1.8	0.2	**143,473**	94.2	1.4	0.0	<0.1	P
Pennsylvania	1995 - 2009	682,922	6.5	1.5	628,121	1.3	0.2	**619,287**	95.7	0.7	0.0	0.0	P
Rhode Island	1995 - 2009	55,914	6.3	0.8	51,937	1.6	0.2	**51,052**	96.0	2.7	0.0	0.0	P
South Carolina	1996 - 2009	184,660	5.3	0.6	173,791	2.0	0.2	**170,159**	94.8	2.0	0.0	0.0	P
Tennessee	2003 - 2009	133,826	5.1	0.9	125,694	2.9	0.2	**122,080**	96.7	0.4	0.0	<0.1	P
Texas	1995 - 2009	814,295	5.0	1.4	762,429	3.2	0.2	**737,811**	94.0	2.5	0.0	0.0	P
Utah	1995 - 2009	63,227	5.9	1.2	58,729	0.4	0.2	**58,373**	97.0	0.4	3.0	0.0	P & A
Washington	1995 - 2008	246,015	5.9	1.3	228,416	1.2	0.2	**225,458**	95.1	0.8	1.9	<0.1	P & A
West Virginia	1995 - 2009	101,396	4.6	1.1	95,644	1.8	0.2	**93,880**	93.6	0.9	0.0	0.0	P
Wisconsin	1995 - 2009	248,955	7.1	1.3	228,035	<0.1	0.3	**227,213**	96.4	2.3	0.0	0.0	P
Wyoming	1995 - 2009	20,934	4.7	0.8	19,797	0.6	0.2	**19,648**	95.6	0.6	0.0	0.0	P & A

Cancer

	Population covered [a]	% of national	Stomach	Colon	Rectum	Liver	Lung	Breast (F)	Cervix	Ovary	Prostate	Leukemia	ALL [b]	Total
Northeast	**53,343,618**	**17.2**	**71,864**	**364,080**	**98,955**	**45,343**	**548,066**	**558,858**	**36,809**	**73,576**	**612,802**	**96,851**	**5,974**	**2,513,178**
Connecticut	3,518,288	1.1	4,890	23,612	6,708	2,817	36,756	39,027	1,987	4,717	41,351	6,435	412	168,712
Massachusetts	6,593,587	2.1	7,881	43,253	12,295	5,223	68,739	73,117	3,524	8,761	75,199	10,951	766	309,709
New Hampshire	1,324,575	0.4	1,119	7,570	2,272	691	12,905	13,540	706	1,608	13,934	2,310	145	56,800
New Jersey	8,707,739	2.8	12,299	59,971	15,731	7,074	86,105	90,804	6,766	12,189	107,252	15,908	1,081	415,180
New York	19,541,453	6.3	27,815	124,529	33,385	18,226	182,745	192,993	14,457	26,279	207,192	34,253	2,113	863,987
Pennsylvania	12,604,767	4.1	16,277	97,350	26,642	10,501	148,024	137,529	8,655	18,753	155,556	25,362	1,388	646,037
Rhode Island	1,053,209	0.3	1,583	7,795	1,922	811	12,792	11,848	714	1,269	12,318	1,632	69	52,753
South	**101,946,182**	**32.9**	**83,760**	**497,182**	**136,823**	**63,616**	**906,514**	**801,768**	**62,815**	**94,898**	**877,756**	**139,280**	**9,699**	**3,674,111**
Alabama	4,708,708	1.5	4,164	25,870	6,761	2,672	47,987	40,510	3,029	5,019	42,472	6,354	384	185,222
Delaware	885,122	0.3	882	5,235	1,471	555	9,670	8,320	605	1,014	10,204	1,320	93	39,369
Florida	18,537,969	6.0	20,634	124,316	31,640	14,460	215,900	184,051	13,971	24,081	217,103	34,954	1,779	882,889
Georgia	9,829,211	3.2	5,038	28,739	8,876	3,764	54,615	52,462	3,905	6,327	57,949	8,344	660	230,679
Kentucky	4,314,113	1.4	3,803	28,207	8,311	2,622	61,642	40,803	3,451	5,062	40,218	7,656	448	202,223
Louisiana	4,492,076	1.5	5,228	27,450	8,001	3,519	49,414	40,902	3,494	4,313	48,372	7,109	443	198,245
Maryland	5,699,478	1.8	4,443	26,837	7,112	3,051	45,181	47,220	2,865	5,364	51,157	6,171	271	199,672
Mississippi	2,951,996	1.0	1,403	8,436	2,353	1,027	15,995	12,124	965	1,327	15,344	2,007	137	61,118
North Carolina	9,380,884	3.0	7,405	46,540	13,170	5,200	88,642	82,085	5,357	9,650	86,701	12,557	909	358,216
Oklahoma	3,687,050	1.2	2,619	19,103	5,209	2,243	37,451	31,244	2,282	3,763	31,251	5,760	373	141,298
South Carolina	4,561,242	1.5	4,129	23,391	6,362	2,429	42,490	38,694	2,932	4,369	45,363	6,045	372	176,576
Tennessee	6,296,254	2.0	2,534	16,679	4,817	1,982	35,098	27,996	1,921	3,113	27,940	4,621	331	127,032
Texas	24,782,302	8.0	19,523	102,010	28,511	18,846	173,838	176,373	16,384	18,903	183,423	32,603	3,330	773,744
West Virginia	1,819,777	0.6	1,955	14,369	4,229	1,246	28,591	18,984	1,654	2,593	20,259	3,779	169	97,828
Midwest	**31,971,621**	**10.3**	**25,906**	**172,649**	**48,545**	**18,747**	**289,855**	**274,527**	**16,538**	**35,847**	**308,883**	**51,542**	**3,095**	**1,246,134**
Iowa	3,007,856	1.0	2,771	22,550	6,012	1,747	32,616	30,562	1,726	4,321	32,471	6,737	348	141,861
Michigan	9,969,727	3.2	10,491	59,825	16,607	7,499	108,252	99,647	6,373	13,398	122,290	18,459	1,136	463,977
Nebraska	1,796,619	0.6	1,670	13,064	3,837	1,226	18,417	19,170	1,229	2,399	20,968	3,929	223	86,132
Ohio	11,542,645	3.7	6,685	43,767	12,779	4,777	80,262	69,842	4,279	8,504	72,251	11,605	726	315,477
Wisconsin	5,654,774	1.8	4,289	33,443	9,310	3,498	50,308	55,306	2,931	7,225	60,903	10,812	662	238,687
West	**62,329,218**	**20.1**	**57,922**	**268,833**	**84,204**	**48,429**	**419,871**	**505,928**	**34,950**	**64,828**	**530,771**	**83,321**	**8,293**	**2,107,350**
Alaska	698,473	0.2	480	2,305	819	450	4,073	4,555	349	470	4,351	649	86	18,587
California	36,961,664	11.9	38,136	162,637	50,069	32,671	249,281	301,418	22,916	38,622	306,346	47,886	5,370	1,255,352
Colorado	5,024,748	1.6	3,214	19,086	5,905	2,696	27,649	39,349	2,375	4,942	41,090	6,703	593	153,602
Hawaii	1,295,178	0.4	2,576	7,559	2,428	1,766	10,079	12,011	825	1,314	11,558	1,685	150	51,951
Idaho	1,545,801	0.5	969	6,058	2,034	580	9,772	11,548	655	1,548	13,922	2,279	181	49,546
Montana	974,989	0.3	860	5,466	1,743	451	9,345	9,336	509	1,243	12,134	1,694	101	42,882
New Mexico	2,009,671	0.6	1,937	8,468	2,765	1,763	12,024	15,681	1,176	1,967	18,460	2,859	274	67,374
Oregon	3,825,657	1.2	2,883	18,637	5,868	2,431	34,325	36,514	1,886	4,537	36,392	5,419	427	149,319
Utah	2,784,572	0.9	1,266	7,430	2,564	864	7,440	14,803	905	2,044	21,057	2,983	353	61,709
Washington	6,664,195	2.2	5,200	28,488	9,253	4,484	51,862	56,176	3,045	7,536	59,414	10,349	708	236,515
Wyoming	544,270	0.2	401	2,699	756	273	4,021	4,537	309	605	6,047	815	50	20,513
US registries	**249,590,639**	**80.6**	**239,452**	**1,302,744**	**368,527**	**176,135**	**2,164,306**	**2,141,081**	**151,112**	**269,149**	**2,330,212**	**370,994**	**27,061**	**9,540,773**

Cancer	All races						White						Black						Difference (%) between				
	Both sexes		Male		Female		Both sexes		Male		Female		Both sexes		Male		Female		Male - Female[b]			Black - White[c]	
	NS (%)	95% CI	NS (%)	95% CI	NS (%)	95% CI	NS (%)	95% CI	NS (%)	95% CI	NS (%)	95% CI	NS (%)	95% CI	NS (%)	95% CI	NS (%)	95% CI	All races	White	Black	Male	Female
Stomach	**29.0**	28.6 - 29.5	**26.5**	25.9 - 27.0	**33.4**	32.7 - 34.1	**28.0**	27.5 - 28.5	**25.3**	24.7 - 26.0	**32.7**	31.8 - 33.5	**28.3**	27.1 - 29.4	**24.5**	23.0 - 25.9	**33.7**	32.0 - 35.4	-6.9	-7.3	-9.2	-0.9	1.0
Colon	**64.6**	64.4 - 64.9	**63.7**	63.3 - 64.0	**65.7**	65.4 - 66.0	**65.4**	65.2 - 65.7	**64.5**	64.1 - 64.8	**66.4**	66.1 - 66.8	**56.6**	55.9 - 57.3	**54.5**	53.4 - 55.5	**58.6**	57.7 - 59.5	-2.0	-1.9	-4.1	-10.0	-7.8
Rectum	**64.0**	63.6 - 64.4	**62.4**	61.8 - 63.0	**66.1**	65.5 - 66.7	**64.2**	63.7 - 64.7	**62.8**	62.1 - 63.4	**66.1**	65.5 - 66.8	**57.5**	56.0 - 59.0	**53.6**	51.3 - 55.9	**61.7**	59.7 - 63.8	-3.7	-3.4	-8.1	-9.2	-4.4
Liver	**14.8**	14.4 - 15.2	**14.3**	13.8 - 14.8	**16.8**	16.1 - 17.6	**14.3**	13.8 - 14.8	**13.8**	13.3 - 14.4	**16.4**	15.5 - 17.3	**11.4**	10.3 - 12.5	**10.8**	9.4 - 12.3	**14.2**	12.2 - 16.2	-2.5	-2.6	-3.4	-3.0	-2.1
Lung	**19.0**	18.8 - 19.1	**16.1**	16.0 - 16.3	**22.4**	22.2 - 22.6	**19.4**	19.2 - 19.5	**16.5**	16.3 - 16.7	**22.7**	22.4 - 22.9	**14.9**	14.5 - 15.2	**12.3**	11.9 - 12.8	**18.3**	17.7 - 19.0	-6.2	-6.1	-6.0	-4.2	-4.3
Breast (F)		-		-	**88.6**	88.4 - 88.8		-		-	**89.6**	89.4 - 89.8		-		-	**78.4**	77.7 - 79.1	-	-	-	-	-11.2
Cervix		-		-	**62.8**	62.2 - 63.5		-		-	**63.5**	62.7 - 64.2		-		-	**55.5**	53.9 - 57.1	-	-	-	-	-7.9
Ovary		-		-	**41.0**	40.5 - 41.5		-		-	**41.7**	41.2 - 42.2		-		-	**31.1**	29.5 - 32.7	-	-	-	-	-10.6
Prostate		-	**96.9**	96.7 - 97.1		-		-	**96.9**	96.7 - 97.1		-		-	**92.7**	92.1 - 93.3		-	-	-	-	-4.2	-
Leukemia	**52.1**	51.7 - 52.5	**52.0**	51.5 - 52.5	**52.3**	51.7 - 52.9	**52.7**	52.3 - 53.1	**52.5**	51.9 - 53.0	**52.9**	52.3 - 53.6	**41.9**	40.4 - 43.5	**41.1**	38.9 - 43.3	**42.7**	40.6 - 44.9	-0.3	-0.4	-1.6	-11.3	-10.2
ALL[d]	**88.1**	87.2 - 88.9	**87.4**	86.2 - 88.6	**88.9**	87.6 - 90.2	**88.6**	87.6 - 89.5	**88.1**	86.8 - 89.4	**89.1**	87.7 - 90.6	**83.6**	80.6 - 86.6	**82.3**	78.4 - 86.2	**85.1**	80.1 - 90.1	-1.5	-1.0	-2.8	-5.8	-4.0

Population-based cancer survival in the US: data, quality control and statistical methods

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Precis for use in the Table of Contents: Population-based cancer survival is a key measure of the overall effectiveness of health systems in managing the cancer burden. The high quality of US cancer registry data, 80% population coverage in the CONCORD-2 study and the use of an unbiased estimator of net survival ensure that the survival trends we report are robustly comparable by race and state. These results can be used to plan and evaluate cancer control strategy, in each state and for the US nationally.

Abstract

Background: Robust comparisons of population-based cancer survival estimates require tight adherence to study protocol, standardized quality control, appropriate life tables of background mortality, and centralized analysis. The CONCORD program established worldwide surveillance of population-based cancer survival in 2015, analyzing individual data on 26 million patients (10 million US patients) diagnosed 1995-2009 with one of 10 common malignancies.

Methods: In this *Supplement*, we analyzed data from 37 state cancer registries covering approximately 80% of the U.S. population that participated in CONCORD-2. We performed data quality checks in three consecutive phases: protocol adherence, exclusions, and editorial checks. We estimated 1-, 3- and 5-year age-standardized net survival using the Pohar Perme estimator and state- and race-specific life tables of all-cause mortality for each year. We adopted the cohort approach for patients diagnosed 2001-2003 and the complete approach for patients diagnosed 2004-2009.

Results Articles in this *Supplement* report population coverage, data quality indicators and age-standardized 5-year net survival by state, race and stage at diagnosis. Examples of tables, bar-charts and funnel plots are provided in this article.

Conclusions Population-based cancer survival is a key measure of the overall effectiveness of services in providing equitable health care. The high quality of US cancer registry data, 80% population coverage and use of an unbiased net survival estimator ensure that the survival trends reported in this *Supplement* are robustly comparable by race and state. The results can be used by policy-makers to identify and address inequities in cancer survival, in each state and for the US nationally.

INTRODUCTION

Population-based cancer survival is a measure of the overall effectiveness of the health system in in dealing with cancer.[1] Comparisons of population-based cancer survival require adherence to a well-designed protocol, standardized quality-control procedures, appropriate life tables of background mortality and centralized analysis with the latest statistical methods.[2, 3]

CONCORD-2 established world-wide surveillance of cancer survival in 2015, with estimates of 5-year net survival based on individual data for more than 25 million cancer patients (about 10 million patients in the US) diagnosed during 1995-2009 with one of ten common cancers: stomach, colon, rectum, liver, lung, breast (female), cervix, ovary, prostate and leukemia in adults (15-99 years), and acute lymphoblastic leukemia in children (0-14 years).[3] Patients were followed up to Dec 31, 2009.

For the articles in this *Supplement*, we analyzed data from 37 statewide cancer registries (27 funded by the National Program for Cancer Registries (NPCR) program, 5 funded by the Surveillance, Epidemiology and End Results (SEER) program and 5 funded by both NPCR and SEER) that participated in CONCORD-2, covering approximately 80% of the U.S. population, and which agreed to the inclusion of their data in more detailed analyses by stage at diagnosis and by race. The CONCORD protocol required data on stage only for patients diagnosed from Jan 1, 2001, therefore these analyses, focused mainly on survival by stage, were restricted to patients diagnosed during 2001-2009.

Public health surveillance using the data from population-based cancer registries is a key component of cancer control.[4] The North American Association of Central Cancer Registries (NAACCR)[a] develops and promotes uniform data standards for all cancer registries in North America. Participating US registries had to meet the NAACCR certification criteria and to have conducted record linkage with both the state vital records and the National Death Index (NDI) to update the vital status of registered patients. NAACCR members developed a detailed SAS program to map the NAACCR database record structure to the CONCORD protocol and thus to enable all North American registries to exclude cases that would not have been considered reportable primaries according to the International Association of Cancer Registries (IACR) multiple primary rules,[5] before their datasets for 1995–2009 were extracted for CONCORD-2. This was necessary because North American registries define

[a] http://www.naaccr.org/standardsandregistryoperations/volumeii.aspx

multiple primary cancers under the rules of the Surveillance, Epidemiology and End Results (SEER) program,[6] whereas registries in the European Network of Cancer Registries (ENCR) and in other continents generally use the rules of the IACR,[5] which are more conservative.

Topography and morphology were coded according to the International Classification of Diseases for Oncology (3rd edition; ICD-O-3[7]). Solid tumors were defined by anatomical site (**Table 1**). For ovarian cancer, we included the fallopian tube, uterine ligaments, and adnexa, and the peritoneum and retroperitoneum, where high-grade serous ovarian carcinomas are often detected; this was done to improve international comparability of the data sets. Kaposi's sarcoma and solid tumors with lymphoma morphology were excluded from analysis.

Leukemias were defined by morphology. In this *Supplement* we cover only precursor-cell acute lymphoblastic leukemia in children (ICD-O-3 morphology codes 9727, 9728, 9729, 9835, 9836, 9837). Estimates of survival by race, state and sub-type of adult leukemia will be presented in other publications.

Only primary invasive cancers (ICD-O-3 behavior code 3) were included in survival analyses. We included cancers at a given site regardless of whether the patient had had a previous cancer. If a patient was diagnosed with two or more cancers of a given organ, including paired organs, during 2001-2009, only the first was considered in survival analyses.

Follow-up

US registries were asked to submit follow-up data (vital status and date of last known vital status) as at Dec 31, 2009, after conducting linkages of all cancer registrations with both state vital records systems and the NDI. Patients whose cancer registration could not be linked to a death record were considered to be alive on Dec 31, 2009 (passive follow-up, also known as the "presumed alive" method).

SEER registries are required to meet a specific standard for the completeness and recency of follow-up. At least 90% of registered patients not known to be deceased were required to have a date of last known vital status on or after Jan 1, 2010. These follow-up dates could have been obtained from either passive or active follow-up.[8]

Patients whose survival time was unknown were excluded from analyses. This group comprised patients registered solely from a death certificate or diagnosed at autopsy.

CONCORD-2 data quality control: three phases

We performed data quality checks in three consecutive phases: protocol adherence, exclusions, and editorial checks. After each phase a detailed report was sent to each cancer registry.

Phase 1: Protocol adherence

We first checked the compliance with the CONCORD-2 protocol of each of 37 variables (demographic characteristics, basis of diagnosis, date of diagnosis, topography, morphology, behavior, stage, vital status, date of last known vital status) in each tumor record in each data set. Any value not specified in the protocol was considered non-compliant. Each registry was sent a table of the number of records and the percentage compliance for each variable, and for each cancer. Minor issues were corrected by the CONCORD Central Analytic Team, after discussion with the registry. For major structural issues, 5 registries corrected and re-submitted their data.

Phase 2: Exclusions

Next, we checked for logical inconsistencies between the variables in each tumor record, for each cancer site. Exclusion criteria were defined *a priori,* based on the experience within the Cancer Survival Group, the checks performed in the first CONCORD study, the EUROCARE (EUROpean CAncer REgistry based study on survival and care of cancer patients) data quality checks, the checks proposed by the International Agency for Research on Cancer (IARC), the descriptions of morphology in the World Health Organization (WHO)/IARC Classification of Tumors for each cancer and, finally, clinical expertise.[3]

We produced "exclusion tables" summarizing the quality of each data set. Data quality indicators were tabulated separately for patients diagnosed in 1995-99, 2000-04 and 2005-09, to enable evaluation of trends in data quality over time. We defined three broad categories for exclusion: ineligible (e.g., *in situ* neoplasm), definite error (e.g., sex-site mismatch) and possible error (e.g., apparent inconsistency between site and morphology). We had requested records of *in situ* neoplasms to assess the intensity of diagnostic activity, particularly for cancers of the breast and cervix, but *in situ* neoplasms were not included in survival analyses. The number and percentage of patients excluded from analysis are shown in **Table 2**.

The majority (99.6%) of patients only had a single tumor record for any one cancer during 1995-2009. However, since a small proportion of patients had more than one tumor record for a given cancer ("multiple tumor, same site"), it was necessary to apply the quality control checks to every tumor record independently before selecting the single tumor record to be included in survival analyses. For example, if a woman had an *in situ* neoplasm of the breast diagnosed in 2001 followed by an invasive primary breast cancer in 2007, the invasive cancer record was selected for inclusion in the analyses, provided it was free of error.

Phase 3: Editorial tables

We evaluated the distribution of key data quality indicators for each cancer and for each registry. These indicators included the proportion of cancers in the final data set that had been microscopically verified and the proportion of patients who had been lost to follow-up. We also checked the distributions of the day and the month of the dates of birth, diagnosis and last known vital status. These distributions should be flat, since one would expect about 8% of births, diagnoses and deaths to occur in each month, and about 3% on each day of a given month, except days 28-31: spikes in these distributions, often on the 1st, 15th or 16th day of the month, or for June or July, help to identify where registries had imputed missing elements of each date.

Table 2 provides a summary of the exclusions and data quality indicators for adults (15-99 years) diagnosed during 1995-2009 with one of 9 common cancers (all solid cancers), by US state. The calendar periods within which survival analyses could be performed by stage at diagnosis were constrained by the availability of data on stage only from 2001, and the change in coding from 2004 (see below). Therefore, the periods for which data quality indicators are presented do not exactly match the periods used for survival analysis. However, data quality has generally been very high in all US registries, and it tended to improve over the 15 years from 1995 to 2009. Only about 2% of tumors were registered from a death certificate only (DCO) or detected solely at autopsy. These records must be excluded from survival analyses because the follow-up time for these patients is unknown. However, the proportion of DCO registrations in the US was low overall (1.9%) and in all states (range: <0.1-3.5%). The proportion of other errors was very low (0.2%). Therefore, about 98% of the eligible patients were included in survival analyses. Practically all tumors (99.7%) were microscopically verified: this proportion was over 95% in almost all US states.

The proportion of the US population covered by this study is 80.6%. **Table 3** shows the population coverage by US state, as well as the number of patients diagnosed during 1995–2009 and included in the analyses.

Study design

The focus of this monograph is on the striking differences in survival by race and stage at diagnosis. Since differences in survival between men and women were generally very small, compared to the differences in survival between blacks and whites (Table 4), we do not show survival estimates by sex in the articles on each cancer.

The CONCORD protocol required information on stage at diagnosis only for patients diagnosed from 2001 onward, because the completeness of data on stage in the US and many other countries was known to be much lower before 2001. For the analyses of survival by stage at diagnosis, patients were grouped by year of diagnosis into two calendar periods (2001-2003 and 2004-2009) to reflect changes in the methods used by US registries to collect data on stage at diagnosis. From 2001, most registries coded stage directly from the source data to SEER Summary Stage (SS) 2000.[9] From 2004, all registries began to derive Summary Stage 2000 from 15 pathological and clinical data items, using the Collaborative Staging System.[10] Data on stage at diagnosis were not available for Maryland or Wisconsin, or for cases diagnosed during 2004-2009 in Rhode Island.

We estimated net survival using the cohort approach for patients diagnosed in 2001-2003, since all patients had been followed up for at least five years by Dec 31, 2009. We used the complete approach to estimate net survival for patients diagnosed from 2004-2009, because five years of follow-up data were not available for all patients.

Cohort approach

The cohort approach is the classical approach to survival analysis, in which all patients who are included in the analyses have had the opportunity to be followed for the full duration of survival analysis, in this case, five years. The cohort of patients is defined by the year or calendar period during which they were diagnosed, and each patient is followed up for the same length of time. In our analyses, at least 5 years of follow-up for vital status were available by the end of 2009 for all patients diagnosed during 2001-2003. Each patient,

irrespective of their actual year of diagnosis, contributes survival information at each point in follow-up time that, taken cumulatively, make up the survival estimate at 5 years.

The cohort approach[11, 12] is considered the gold standard,[11, 12] because it provides a survival estimate for a group of patients who were diagnosed during the same year or period, who are likely to have been treated in similar fashion, and who have all been followed up for at least the duration of survival required. It is the natural approach to estimation of outcome, and is easy to interpret, but other approaches may be required if sufficient data are not available.

Complete approach

The complete approach can be applied to estimate survival for patients who were diagnosed more recently, and for whom 5 full years of follow-up data may not be available at the closing date of the study. For example, some patients diagnosed 2004-2009 were followed up for less than 5 years. The 'cohort' approach can be used to estimate five-year survival for patients diagnosed in 2004, but 5-year survival can be estimated for the whole calendar period with the 'complete' approach, in which all the available follow-up data for patients diagnosed during 2004-2009 are used. The potential follow-up time for these patients varies between 1 year and 5 years.

Age standardization

We compared survival estimates between US states, between blacks and whites, and between calendar periods of diagnosis. For age-specific survival estimates, comparison between populations or over time is straightforward, but if we want to compare overall (all-ages) survival estimates, age standardization is required. This is essentially for the same reasons as in comparison of overall incidence or mortality rates, namely that net survival may also vary widely with age at diagnosis, and the age profile of cancer patients may differ between the populations or change between the calendar periods among which we wish to compare overall survival.

For age-standardization of incidence or mortality rates, what matters is the age structure of the general population at risk of cancer. With cancer survival, however, what matters is the age profile of cancer patients, which is very different from the age profile of the general population. The weights used for age standardization of cancer survival estimates are thus completely different from those required for standardizing incidence or mortality rates. The

weight for each age group is provided by the proportion of cancer patients in that age group in a standard population of cancer patients.

The International Cancer Survival Standard (ICSS) weights[13] are strongly recommended for international comparisons of cancer survival. They comprise three sets of standard age weights, derived from discriminant analysis to find the smallest number of sets of weights that enable adequate standardization of survival. Each standard is applicable to a range of different cancers, and provides age-standardized survival estimates that are not too different from the unstandardized estimates. The same age weights can be used for men and women, and for direct comparisons of age-standardized net survival between patient groups defined by sex and race.

Statistical methods

We estimated net survival up to 5 years after diagnosis, with 95% confidence intervals (CI), using the Pohar Perme estimator,[14] implemented in the *Stata*[15] algorithm *stns*.[16] We analyzed survival by state, race, stage at diagnosis and calendar period of diagnosis. Net survival is the probability of surviving up to a given time since diagnosis after controlling for other causes of death (background mortality). To control for the wide differences in background mortality among participating states and racial/ethnic groups, we constructed life tables of all-cause mortality in the general population of each state from the number of deaths and the population, by single year of age, sex, calendar year and, where possible, by race (black, white).

Net survival in adults was estimated for five age groups (15-44, 45-54, 55-64, 65-74, and 75-99 years; except for prostate cancer 15–54, 55–64, 65–74, 75–84 and 85–99 years). We obtained age-standardized survival estimates using the International Cancer Survival Standard (ICSS) weights. For children, survival was estimated for the age groups 0–4, 5–9 and 10–14 years. We obtained age-standardized estimates by assigning equal weights to the three age-specific estimates.[17]

We derived standard errors for both unstandardized and age-standardized survival estimates using the Greenwood method,[18] assuming a normal distribution, and truncated to the range 0–100. We did not estimate survival if fewer than ten patients were available for analysis. Age-standardization was only performed if there were at least 10 patients in each of the age

categories specified above. If an age-specific estimate could not be obtained, we merged data for adjacent age groups and assigned the combined estimate to both age groups. If two or more age-specific estimates could not be obtained, we present only the pooled, unstandardized estimate for all ages combined: these estimates are italicized in Tables 2 and 3 of the Appendix.

For each of the 37 states, we present estimates of age-standardized net survival for each cancer up to 5 years after diagnosis. For convenience, we report cumulative survival probabilities (in the range 0-1) as percentages in the range 0-100%.

Life tables

For the analyses presented in this *Supplement*, we used the life tables for background mortality that were constructed for the CONCORD-2 study.[19]

To control for variation between US states in background mortality by age, sex, race and calendar year while estimating net survival, we used life tables of all-cause mortality rates by single year of age (0-99 years), for each state, race, calendar year (2001-2010) and sex. For a few states in which the black population is small, it was not possible to construct adequately robust life tables of all-cause mortality by single year of age and sex for blacks, so net survival estimates for blacks in those states are not presented separately. These life tables can be downloaded from the CONCORD library of over 12,000 life tables.[20] The library includes detailed statistical and graphical reports on the robustness of the life tables for each US state.

We received raw data on death counts and populations for each US state. To produce life tables for each US state by race, sex and calendar year (state- and race-specific life tables) we used a flexible Poisson model[21] that enables creation of single-year-of-age life tables even when the raw data are sparse. We checked the life tables by examination of semi-log plots of age-sex-mortality rates, life expectancy at birth, the probability of death in the age bands 15–59, 60–84 and 85–99 years and, where necessary, the model residuals, to examine the goodness of fit of the models by age and sex.

Graphical representation

In each cancer-specific article in this *Supplement*, trends, geographic variations and differences in age-standardized survival by race are presented graphically in bar-charts and funnel plots.[22]

Bar-charts

Results were summarized in bar-charts of 5-year age-standardized net survival by calendar period (2001-2003 and 2004-2009), for each state, grouped within the four US geographic Census Regions (Northeast, South, Midwest, West). The results for each Region are presented with a different color. Within each Region, darker shades indicate NPCR registries, while lighter shades indicate SEER registries. Five registries funded by both SEER and NPCR were grouped with SEER because they use both passive and active follow-up; they are indicated with an asterisk "*".

The survival estimates for each state in 2004-2009 are ranked from high to low within each US Census Region. The same ranking is then applied to the results for 2001-2003, to facilitate examination of changes in survival from 2001-2003 to 2004-2009 within each state. The absolute difference (%) in 5-year net survival between the two periods is also shown for each state.

Each graphic includes the pooled survival estimates for all 37 participating states combined.

Funnel plots

Funnel plots are graphical representations designed to detect excessive variation in performance indicators by simple visual inspection of the data.[23] They can be used to provide a simple and informative display of geographical variation or time trends in population-based cancer survival measures (e.g. age-standardized net survival).

A funnel plot comprises four elements:[22] the target (or reference) value for the outcome, a set of control limits (the funnel), data points for the outcome variable (indicator) and the associated precision parameter for each data point. Data points outside the control limits (the funnel) indicate variation in the indicator beyond what would be expected by chance, while taking account of precision.[23]

The funnel plot in Figure 1 shows, as an example, 5-year age-standardized net survival for breast cancer in the US during 2004-2009, by race and state. It is constructed by plotting the 37 state-specific survival estimates for breast cancer during 2004-2009, on the y-axis, against

their associated precision, on the x-axis, forming a scatter plot. Fewer data points are available for blacks (28 states) than for whites (37 states), because of the difficulty in constructing robust life tables for blacks in every state. The precision parameter in this example is in fact the precision of each age-standardized net survival estimate (the inverse of its variance). This is a natural choice to represent the statistical precision of each estimate, but it could be any function that is proportional to the inverse of the variance.

The target (the solid horizontal line in Figure 1) is then superimposed. This is a constant value, considered independent of the observations, and it specifies the expected value for the outcome. The target shown in Figure 1 is the 5-year age-standardized net survival estimate for the pooled US data for women diagnosed with breast cancer during 2004-2009. The pooled US estimate was selected as the target to show the extent to which survival for blacks and whites in each state varies around the overall survival estimate for the US.

The control limits (the dashed lines in Figure 1) are also independent of the individual survival estimates. They depend only on the target value, and their correct formulation depends on the underlying theoretical distribution of the target value. The control limits for a given level of significance (α) are drawn around the target value across the entire observed range of precision of the individual estimates. The most common levels of significance are α=5% and α=0.2%, so that the resulting 95% and 99.8% control limits represent approximately two and three standard deviations, respectively, on either side of the target value, at each level of precision. An estimate that appears outside the control limits is identified as diverging from the target value, and is an "out-of-control" estimate, in other words a probable outlier that may need to be investigated further.

In Figure 1, as with all the funnel plots reported in this *Supplement*, 5-year age-standardized net survival is represented by open circles for white patients and by solid circles for black patients. Funnel plots are extremely powerful tools for visual examination of variation in an indicator: we can perceive at first glance that 5-year survival in blacks is persistently lower than would be expected (the pooled US survival estimate, the "target") and that survival for blacks is generally lower than for whites.

DISCUSSION

This article summarizes the data quality control procedures, analytic methods and graphical presentations that have been deployed for all the data sets reported in this *Supplement*. The quality of population-based data from the 37 participating US cancer registries was impressively high (Table 2). More details about the quality indicators for each cancer can be found in the web-appendix[b] to the CONCORD-2 article.[3]

For NPCR registries that use only passive follow-up to determine the vital status of registered cancer patients (the "presumed alive" method), survival estimates may be inflated if the cancer registrations for some patients who have in fact died could not be successfully linked to the data from their death certificate. The vital statistics offices in each state have reported all death certificate information to the National Death Index (NDI) since 1979. Passive methods of follow-up are known to be efficient because of the completeness and accuracy of the National Death Index, which tends to capture 1-3% more deaths than if the registry can only link its data to the state death index[24]. Most of the extra deaths captured in this way will be those of patients who migrated to a different state following their cancer diagnosis. However, the registries included in these analyses had all matched their data against the National Death Index before data submission, so the completeness of vital status ascertainment is expected to be extremely high, although it may not capture out-of-country deaths.

A major strength of this study is the use of life tables that are specific for each state, each race (white, black) and each calendar year, to control for differences and changes in background mortality by single year of age, sex, race and single calendar year. This approach provided the tightest possible control of background mortality with the available data. More specific life tables may be considered in future studies, subject to the availability of high-quality data on death and population counts for Hispanics or other major racial or ethnic groups.

The CONCORD-2 protocol required registries to provide information on stage at diagnosis for patients diagnosed in 2001 or later. Calendar years of diagnosis were then grouped for analysis of survival by stage into 2001-2003 and 2004-2009, to reflect a change in the US stage coding system from 2004.

This choice of calendar periods imposed the following selection of analytic approach. We were able to estimate 5-year net survival with the cohort approach for patients diagnosed in 2001-2003, since all patients had at least 5 years of potential follow-up. However, the period

[b] http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(14)62038-9/supplemental

approach[25] that was adopted to estimate 5-year survival for patients diagnosed 2005-2009 in the CONCORD-2 study[3] could only have been used to estimate 5-year survival by stage for patients diagnosed during 2004-2009 if stage data had also been available for patients diagnosed in 2000. We therefore adopted the complete approach. In this approach, more information is available to estimate survival in the early years of follow-up than later years. Only patients diagnosed in 2004 had the potential to be followed up for 5 years by Dec 31, 2009; only patients diagnosed during 2004 and 2005 had the potential to contribute to the conditional survival probabilities between 4 and 5 years after diagnosis; and so on. This leads to some increased variation around the 5-year survival estimates for 2004-2009 compared with those for 2001-2003. This is reflected in the confidence intervals, and slightly lower precision, seen in the funnel plots for 2004-2009 in some of the site-specific articles.

This is the most extensive analysis of 5-year population-based cancer survival in the US to date, with survival trends for 10 common cancers in 37 states that include 80% of the US population. Here, we have focused on variations in survival by race and stage at diagnosis for patients diagnosed during 2001-2009.

Population-based cancer survival is a key measure of the overall effectiveness of the health system in in dealing with cancer. The high quality of the data from the US cancer registries, implementation of the most up-to-date and unbiased estimator of net survival, combined with the use of state- and race-specific life tables, all help to ensure that these cancer survival estimates are robust and comparable. We believe they can be confidently used by policy-makers to identify inequities in cancer survival by race in each state and for the US as a whole, and to plan cancer control strategies that promote equal opportunity for the best possible outcomes after a cancer diagnosis.

Legends for Tables and Figures

Table 1 Definition of malignancies

Table 2 Data quality indicators for patients diagnosed during 1995–2009, by US state (all solid cancers combined)

Table 2 footnotes:

[a] *In situ* malignancy (ICD-O-3 behavior code 2): some registries do not register in situ cancers; other registries did not submit them. Other: records with incomplete data, or for tumors that are benign (behavior code 0), of uncertain behavior (1), metastatic from another organ (6), or unknown if primary or metastatic (9); or for patients with age outside the range 15-99 years (adults).

[b] DCO: tumors registered from a death certificate only (DCO), or detected solely at autopsy. Other: vital status or sex unknown; invalid sequence of dates; inconsistency of sex-site, site-morphology, age-site, age-morphology, or age-site-morphology.

[c] MV: microscopically verified. Non-specific morphology (solid tumors only): ICD-O-3 morphology code in the range 8000-8005. Censored: patients diagnosed during 1995-2004, with last known vital status "alive", but less than five years of follow-up.

[d] P=Passive ("presumed alive") method; P&A=Passive and Active ("reported alive") methods; see text.

Table 3: Population coverage and number of patients diagnosed during 1995–2009, by US state

Table 3 footnotes:

[a] Data are from the UN Population Division for 2009

[b] Acute lymphoblastic leukemia, children (0-14 years) only

Table 4: Age-standardized 5-year net survival (NS, %) for adults (15-99 years) diagnosed with one of 10 common malignancies and children (0-14 years) diagnosed with acute lymphoblastic leukemia (ALL) during 2004-2009, by race and sex: United States[a]

Table 4 footnotes:

[a] Population coverage represents 80.6 % of the US population in 2009 (UN Population Division)

[b] A negative value means that males have lower survival than females

[c] A negative value means that blacks have lower survival than whites

[d] Acute lymphoblastic leukemia, children (0-14 years) only

Figure 1: 5-year age-standardized net survival for women (15-99 years) diagnosed with breast cancer in 2004-2009, by state and race

Figure 1 footnote: Each data point represents the survival estimate for a US state, either for blacks (28 states) or whites (37 states; see text).

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