

## **Population-Based Cancer Survival (2001–2009) in the United States: Findings from the CONCORD-2 Study**

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**Running title:** US population-based cancer survival (2001-2009)

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**Precis:** The Centers for Disease Control and Prevention helps support a nationwide network of population-based cancer registries that collect information on all patients diagnosed with cancer. These data tell a compelling story about the disproportionate burden of lower cancer survival experienced by vulnerable populations, and can be used by state and national partners to inform cancer control activities.

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## INTRODUCTION

In this *Supplement [Population-based Cancer Survival in the United States (2001-2009): findings from the CONCORD-2 study]* we provide survival estimates by race (black, white), state of residence at diagnosis and stage at diagnosis for nine solid tumors in adults<sup>1-9</sup>, and for acute lymphoblastic leukemia in children (ALL).<sup>10</sup> Data are from 37 statewide cancer registries that participated in the CONCORD-2 study,<sup>11</sup> covering 80% of the US population. Each of the 10 cancer-specific papers includes clinical and cancer control perspectives. These perspectives highlight how clinical practice may have had an impact on population-based cancer survival trends, and how states funded by the Centers for Disease Control and Prevention (CDC)'s National Comprehensive Cancer Control Program<sup>12</sup> can use population-based survival data, along with incidence and mortality data, to inform cancer control activities.<sup>13</sup>

### *The Growing Cancer Burden*

Cancer may soon become the leading cause of death in the United States: it is already the leading cause in nearly half of all states.<sup>14</sup> While the risk of dying from cancer continues to decrease, as measured by the age-standardized death rate, the actual number of cancer deaths continues to increase.<sup>15</sup> This increase is being driven, to a large extent, by demographic trends related to a growing and aging U.S. population. By 2020, nearly 2 million men, women, and children will be diagnosed with cancer annually.<sup>16</sup> In addition, the number of people living with and after a cancer diagnosis (cancer survivors) will also increase from an estimated 14 million in 2012 to 18 million by 2022.<sup>17</sup> Cancer survivors remain at risk for recurrence of their cancer, development of subsequent new cancers, and side-effects related to their cancer treatment.<sup>18</sup>

Prevention of many of these cancers is possible through behavioral, environmental, policy, and clinical interventions to address the wide range of factors that put people at increased risk of developing cancer over their lifetime.<sup>19</sup> However, even if all known effective strategies for cancer prevention were broadly implemented today, the impact on cancer incidence would likely not be seen for several decades, due to the long latency period for many cancers. The anticipated increase in the number of new cancer patients

and survivors poses an enormous challenge for the US health care system to meet the need to screen, diagnose, and treat these patients.<sup>21,22</sup> It is also a major challenge to the public health community to help cancer patients meet the financial, physical and psychological challenges related to their cancer experience, including difficulties in returning to full economic activity.<sup>22,23</sup>

To address the challenge of the growing cancer burden, the CDC's Division of Cancer Prevention and Control (DCPC) collaborates with state and national partners to implement public health strategies to promote primary prevention, cancer screening, early diagnosis, and access to effective evidence-based treatment and survivorship care plans.<sup>12</sup> The challenge for the public health community is to put in place primary prevention and early detection strategies for the general population while meeting the growing needs of cancer patients and survivors.

### ***Cancer Surveillance in the US***

In the United States, cancer control activities primarily take place at the state and local levels, and cancer control planners need information on the unique cancer burden in their states. Cancer is the only reportable chronic disease in the country for which there is nationwide surveillance.<sup>24</sup> There is now a population-based cancer registry in all 50 states and the District of Columbia.<sup>12</sup> In addition to state support, these registries receive federal support from the CDC's National Program of Cancer Registries (NPCR) and the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) Program. These registries provide a census of all people diagnosed with cancer, and along with state vital records offices, collect and report a basic set of information on all new cancer cases (incidence), deaths (including cancer-caused), the number of cancer patients alive in a given calendar period (prevalence) and the probability of being alive up to a given point in time after diagnosis (survival).

Population-based cancer survival differs in a fundamental way from the survival of cancer patients participating in clinical trials.<sup>25,26</sup> Population-based survival reflects the average survival for *all* cancer patients in the population, regardless of their age, sex,

race, health status, stage of disease, socioeconomic position, residence at diagnosis and access to care. As such, population-based cancer survival provides an indicator of the overall effectiveness of the health care system to deliver screening, early diagnosis, and evidenced-based treatment services and follow-up care to all people in the population being served.<sup>25-27</sup>

### ***The CONCORD Programme***

The CONCORD Programme at the London School of Hygiene and Tropical Medicine established worldwide surveillance of population-based cancer survival in 2015.<sup>11,25</sup> The first CONCORD study provided a systematic comparison of survival for patients aged 15-99 years diagnosed with a cancer of the female breast, colon, rectum, or prostate between 1990 and 1994.<sup>28</sup> International differences in 5-year age-standardized survival were wide, even after adjustment for differences in mortality from other causes of death. Survival in the United States was among the highest in the world. However, the study reported large and consistent black and white racial disparities in survival for all four cancers in the United States (**Table 1**). For example, survival for black women diagnosed with breast cancer was 14% lower than survival for white women, and ranked, along with breast cancer survival in the United Kingdom, just above survival in eastern European countries, but lower than survival in northern and western European countries.

The CONCORD-2 study estimated long-term survival trends among 25.7 million individual cancer patients in 67 countries who were diagnosed during the 15-year period 1995-2009 with one of 10 common cancers [stomach, colon, rectum, liver, lung, female breast, cervix, ovary, prostate and leukaemia (including children)].<sup>11</sup> As reported in the first CONCORD study, international differences in age-standardized survival were wide, even after adjustment for differences in mortality from other causes of death. Survival in the United States for most cancers was again among the highest in the world.

The cancer survival estimates presented in the 10 cancer-specific papers included in this Supplement come from more detailed analysis of the data contributed to the CONCORD-2 study.<sup>11</sup> A description of the data from the 37 participating cancer registries, and the

rigorous and advanced statistical methods used to evaluate and analyze the data, are presented in an accompanying paper.<sup>29</sup> We focused on patients diagnosed during two calendar periods (2001-2003 and 2004-2009), because the method used by U.S. cancer registries to collect and report anatomic stage (SEER Summary Stage 2000) changed beginning January 1, 2004. We observed 5-year survival to be high ( $\geq 80\%$ ) for breast cancer in women<sup>6</sup>, prostate cancer<sup>9</sup> and acute lymphoblastic leukemia (ALL) in children<sup>10</sup>; moderate (50-80%) for cancers of the colon<sup>3</sup>, rectum<sup>2</sup> and cervix<sup>7</sup>, and low ( $< 50\%$ ) for cancers of the stomach<sup>1</sup>, liver<sup>4</sup>, lung<sup>5</sup> and ovary<sup>8</sup> (**Table 1**). These observations are consistent with those of long-term trends in survival in the United States for many leading cancers in both adults and children.<sup>30</sup> The comparison of survival by calendar period in the cancer-specific papers in this Supplement shows that even over this relatively short time period, survival has improved for cancers that were highly lethal (stomach<sup>1</sup>, liver<sup>4</sup>, lung<sup>5</sup>, and ovary<sup>8</sup>). However, less progress was observed for cancers where survival was already moderate to high, likely reflecting previous gains achieved from screening (colon<sup>3</sup>, rectum<sup>2</sup>, breast<sup>6</sup>, and cervix<sup>7</sup>) or where treatment was already highly effective (ALL)<sup>10</sup>. The high survival for prostate cancer likely reflects the use of the prostate-specific antigen test for early detection of cancer, which was recommended by the American Cancer Society during this time period.<sup>31</sup> The potential impact of over-diagnosis was also evident in these data, where 5-year survival following a diagnosis of locally staged prostate cancer in black and white men<sup>9</sup>, and breast cancer in white women<sup>6</sup>, was close to 100%.

But, as the results from this Supplement also show, the large racial disparities in cancer survival between blacks and whites in the United States are consistent across all 37 states participating in the CONCORD-2 study, and they persist over time (**Table 1**). With the exception of stomach cancer, 5-year survival was lower in black men and women than in white men and women for all solid tumors examined. The funnel plots in the accompanying articles for female breast<sup>6</sup>, colon<sup>3</sup> and ovarian<sup>8</sup> cancers show just how large and consistent these disparities were across the 37 states.

Each of the accompanying papers contains bar charts of 5-year survival for all races combined for each state and each calendar period, grouped by US Census Region. Some patterns of regional variation were observed. Survival in several Northeastern states tended to be somewhat higher than the pooled US estimate, while survival in several of the Southern states tended to be somewhat lower than the pooled US estimate. As expected, some variation in survival among the states was observed, likely due at least in part to racial and socio-economic disparities.

Findings from these analyses may help explain why overall survival in the United States is among the highest, compared to other high-income countries, as reported in both the first CONCORD study and the CONCORD-2 study. The overall high percentage of microscopically verified cancers observed for all cancers<sup>29</sup>, and the relatively low percentage of patients with solid tumors for whom stage at diagnosis was unknown<sup>1-9</sup>, suggests that detailed clinical investigation at diagnoses was performed for most cancer patients diagnosed during this time period. But the large and consistent racial disparities described herein are likely due to the fact that cancers diagnosed in black men and women tended both to be diagnosed at a later stage and to have lower survival at each stage of diagnosis.<sup>1-9</sup> These disparities often appeared in the first year following diagnosis, suggesting that additional factors, such as co-morbidities and socio-economic factors related to limited access to screening, diagnosis, treatment and follow-up care, may be relevant.

### ***How these data can be used by cancer control programs***

Population-based survival data have been used to plan and evaluate national cancer control strategies in the United Kingdom.<sup>32,33</sup> In the United States, these data can be used by state-based programs to help target and evaluate cancer control strategies promoting screening (colon, rectum, cervical, breast)<sup>12</sup> and symptom awareness for gynecologic cancers (ovary).<sup>34</sup> It should be noted that survival for women diagnosed with localized ovarian cancer is also high<sup>8</sup> and future research that focuses on the development of new methods or modalities to detect these cancers whilst they are still at a local stage may well improve overall ovarian cancer survival. For cancers with low overall survival

(stomach, liver, lung and ovary), efforts directed at reducing cancer incidence through primary prevention, where such strategies exist, are likely to have the greatest impact on reducing the cancer burden in the longer term.

Between the first CONCORD study (1990-1994) and the CONCORD-2 study (1995-2009), survival in the United States improved for female breast, colon, rectum and prostate cancers (**Table 1**). However, 5-year survival for cancers of the colon diagnosed among black men and women during 2004-2009 had yet to reach the levels of survival seen for white men and women diagnosed during 1990-1994, some 10 to 15 years earlier. Similar findings were observed for breast cancer in women and rectal cancer in men, where survival in blacks lagged approximately 15 years behind survival in whites. If equal access to medical care, including screening, diagnosis and treatment services, yield equal outcome, *regardless of race*,<sup>35-37</sup> these disparities represent a large number of potentially avoidable premature deaths which, in turn, impose a large economic burden on affected communities.<sup>38</sup>

The findings of large, consistent and persistent racial disparities in survival should compel robust action. Results from the first CONCORD study showed that breast cancer survival in the UK was lower than in comparable European countries. This prompted the Department of Health in England to initiate the International Cancer Benchmarking Partnership study (ICBP) with the aim to examine international variation in cancer survival for a number of leading cancers, and to inform health policy to improve cancer survival through an examination of population awareness and beliefs about cancer; attitudes, behaviors and systems in primary care; delays in diagnosis and treatment, and their causes; and treatment, co-morbidities and other factors.<sup>39-42</sup> A similar comprehensive and coordinated initiative at the local and state level in the United States might help us identify the strategies and actions needed to achieve the highest possible survival for all men and women diagnosed with cancer, regardless of their race, ethnicity and socio-economic position.

### ***Strengths and Limitations***

There are inherent strengths and limitations in studies performed using data from population-based cancer registries. The high quality and completeness of the US data, and the rigor of the analytic methods used, ensured that the survival estimates reported in this Supplement are directly comparable between participating states. In the US, all cancer registries are members of the North American Association of Central Cancer Registries (NAACCR) and they collect and report incidence data using common procedures and the same data dictionary.<sup>12</sup> The CONCORD-2 study maximized the comparability of the results by using a common protocol for data submission, with standardized quality control procedures and centralized analysis, including advanced statistical methods and the construction of state-, race- and sex-specific life tables of all-cause mortality by single year of age and single calendar year, to correct for differences in background mortality. All participating registries met NAACCR certification criteria with respect to the completeness and quality of their incidence data, including ascertainment of cases. Therefore, the findings do not reflect case ascertainment bias wherein patients with very poor prognosis and shorter survival (e.g., advanced disease, clinical diagnosis) are less completely captured by the cancer registries than patients with good prognosis and longer survival.

Several limitations could impact the interpretation of the findings. While survival data have been shown to be comparable when death ascertainment is complete<sup>42</sup>, follow-up procedures among cancer registries in the United States differ depending on federal funding source.<sup>12</sup> SEER registries are required to conduct active follow-up of all registered cases to ascertain vital status while NPCR registries are only funded to conduct linkage with their state vital records to obtain information on deaths that occurred within their state and with the CDC's National Death Index to obtain information on deaths that occurred anywhere within the United States. As a result, NPCR registries may miss some deaths, particularly for patients who leave the United States between the time of their diagnosis and death, and slightly overestimate the patient's survival time.<sup>44</sup> This limitation may account for the somewhat higher survival estimates for several large (population) NPCR registries which were most evident in the funnel plots of highly fatal cancers where missing deaths could lead to an overestimate of survival.<sup>45</sup> Second, this

was the first opportunity for several NPCR registries to collect and report survival data, which may account for some of the state variability observed, particularly in the first (2001-2003) calendar period. The reluctance of some medical facilities to report social security numbers and complete dates of birth to their state cancer registry may have impeded a registry's ability to identify deaths through subsequent linkages with state and national death certificate files. Third, the manner in which SEER Summary Stage 2000 data were collected and reported changed for all registries in 2004. The impact of this change was most evident among NPCR-funded registries, which coded stage data manually in the first calendar period (2001-2003) and then derived stage data in the second period (2004-2009); the percentage of cases with unknown stage decreased slightly beginning around 2004. Lastly, analyses of survival by race were restricted to whites and blacks, the two major racial groups in the United States, because life tables for other races and Hispanics were not available.

### **Future Plans**

The CONCORD-3 study is in progress. It will update world-wide surveillance of cancer survival trends to include patients diagnosed through 2014.<sup>26</sup> It will include 15 malignancies that collectively represent 75% of the global cancer burden: esophagus, stomach, colon, rectum, liver, pancreas, lung, melanoma, breast (women), cervix, ovary and prostate in adults (15-99 years), and brain tumors, lymphomas and leukemias in both adults and children (0-14 years). The US contribution is expected to cover 44 states and up to 90% of the national population.

### **Conclusion**

The quality of the CONCORD-2 data, the rigorous statistical methods used and the large population coverage provide a broad and comprehensive overview of trends in survival among cancer patients diagnosed up to 2009. They provide a valuable contribution to public health and cancer control in the United States. These data benchmark the status of population-based cancer survival immediately prior to the implementation of the Affordable Care Act in 2010. Further improvements in survival may result from collaborations with state and national partners to implement public health strategies to

promote cancer screening, early diagnosis, access to effective evidence-based treatment (including personalized cancer care and targeted therapies), and follow-up care. The Division of Cancer Prevention and Control can help improve access to timely diagnosis and treatment through its screening programs, awareness campaigns and by facilitating the implementation of long-term survivorship care plans.<sup>12</sup>

The challenge will be to ensure that everyone diagnosed with cancer in the United States benefits equally from advances in diagnosis and treatment.

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Table 1 5-year age-standardized population-based survival by calendar period of diagnosis, cancer site and race (black, white).

Site	Sex	CONCORD (1990-94) <sup>a</sup>			CONCORD 2 (2004-2009) <sup>b</sup>		
		Black	White	Difference	Black	White	Difference
Stomach	Both	NA	NA	NA	28.3	28.0	<b>0.3</b>
Colon	Men	51.5	60.5	<b>-9.0</b>	54.5	64.5	<b>-10.0</b>
	Women	51.0	60.8	<b>-9.8</b>	58.6	66.5	<b>-7.9</b>
Rectum	Men	47.4	57.3	<b>-9.9</b>	53.6	62.8	<b>-9.2</b>
	Women	49.4	60.4	<b>-11.0</b>	61.8	66.2	<b>-4.4</b>
Liver	Both	NA	NA	NA	11.4	14.3	<b>-2.9</b>
Lung	Both	NA	NA	NA	14.9	19.4	<b>-4.5</b>
Breast	Women	70.9	84.7	<b>-13.8</b>	78.4	89.7	<b>-11.3</b>
Cervix	Women	NA	NA	NA	55.5	63.5	<b>-8.0</b>
Ovary	Women	NA	NA	NA	31.1	41.7	<b>-10.6</b>
Prostate	Men	85.8	92.4	<b>-6.6</b>	92.7	96.9	<b>-4.2</b>
ALL	Both	NA	NA	NA	83.6	88.6	<b>-5.0</b>

NA – not applicable.

Source: <sup>a</sup> Coleman et al. 2008 (ref # 28) ; <sup>b</sup> Allemani et al. 2017 (ref #11, 29).