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SCREENING OF INFANTS AND MORTALITY DUE TO NEUROBLASTOMA

WILLIAM G. WOODS, M.D., RU-NIE GAO, M.D., JONATHAN J. SHUSTER, PH.D., LESLIE L. ROBISON, PH.D., MARK BERNSTEIN, M.D., SHEILA WEITZMAN, M.D., GRETA BUNIN, PH.D., ISRA LEVY, M.D., JOSEF BROSSARD, M.D., GEOFFREY DOUGHERTY, M.D., MENDEL TUCHMAN, M.D., AND BERNARD LEMIEUX, M.D.

ABSTRACT

Background Neuroblastoma, the most common extracranial solid tumor that occurs in early childhood, can be identified in the preclinical stages by the detection of catecholamines in the urine. However, it is unknown whether routine screening for neuroblastoma reduces mortality due to this disease.

Methods Through their parents, we offered screening for neuroblastoma at three weeks and six months of age to all 476,654 children born in the province of Quebec, Canada, during a five-year period (May 1, 1989, through April 30, 1994). The participation rate was 92 percent. The rate of death due to neuroblastoma was determined and compared with the rates in several unscreened control populations born during the same period.

Results Among children younger than eight years of age in the Quebec cohort, there were 22 deaths due to neuroblastoma; the cumulative (\pm SE) mortality rate due to neuroblastoma was 4.78 ± 1.14 per 100,000 children over a period of nine years. The standardized incidence ratios for death due to neuroblastoma for the Quebec cohort were 1.11 (95 percent confidence interval, 0.64 to 1.92) as compared with a control group in Ontario, Canada; 0.90 (95 percent confidence interval, 0.48 to 1.70) as compared with a control group in Minnesota; 1.40 (95 percent confidence interval, 0.81 to 2.41) as compared with a control group in Florida; and 0.96 (95 percent confidence interval, 0.56 to 1.66) as compared with a control group in the Greater Delaware Valley. The standardized mortality ratio for the Quebec cohort as compared with the rest of Canada was 1.39 (95 percent confidence interval, 0.85 to 2.30); the odds ratio for the comparison with a cohort born in Quebec before the screening program began was 0.98 (95 percent confidence interval, 0.54 to 1.77).

Conclusions Screening infants for neuroblastoma does not appear to reduce mortality due to this disease. (N Engl J Med 2002;346:1041-6.)

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NEUROBLASTOMA, the most common extracranial solid tumor in children under the age of five years, affects 1 in 7000 children.¹⁻³ Forty percent of cases are diagnosed in children younger than one year of age. These young children have an extremely favorable prognosis even if they present with metastatic disease. This observation has led to consideration of screening infants with the use of specific catecholamine markers that may be measured easily in urine in order to detect the disease in preclinical stages.^{4,5} However, it is not known whether this approach can reduce mortality from neuroblastoma.^{6,7}

We designed the Quebec Neuroblastoma Screening Project to determine whether the detection of preclinical neuroblastoma in a large, geographically defined population of infants could lead to lower mortality from this disease than that found in several large population-based control groups who were not offered screening.^{8,9} We have previously shown that screening for neuroblastoma results in the detection of twice as many cases of the disease as would be expected without decreasing the incidence of advanced-stage disease among older children.¹⁰

METHODS

The Screened Quebec Cohort

A description of the design of this study was published previously.⁸⁻¹⁰ We selected the province of Quebec, Canada, for the

From the AFLAC Cancer Center, Emory University and Children's Healthcare of Atlanta, Atlanta (W.G.W.); Statistics Canada, Ottawa, Ont. (R.-N.G.); University of Florida, Gainesville (J.J.S.); University of Minnesota, Minneapolis (L.L.R.); Hôpital Sainte-Justine, Montreal (M.B.); Hospital for Sick Children, Toronto (S.W.); Children's Hospital of Philadelphia, Philadelphia (G.B.); Canadian Medical Association, Ottawa, Ont. (I.L.); Centre Universitaire de Santé de l'Estrie, Sherbrooke, Que., Canada (J.B., B.L.); Montreal Children's Hospital, Montreal (G.D.), and Children's National Medical Center, Washington, D.C. (M.T.). Address reprint requests to Dr. Woods at the AFLAC Cancer Center, Emory University and Children's Healthcare of Atlanta at Egleston, 1405 Clifton Rd., NE, Rm. 319, Atlanta, GA 30322, or at william.woods@choa.org.

study because it was the only place in North America with an extensive preexisting infrastructure for collecting the urine of infants on filter papers.¹¹ Through their parents, all children born in the province during a five-year period (May 1, 1989, to April 30, 1994) were offered free screening for neuroblastoma by measurement of urinary homovanillic acid and vanillylmandelic acid (metabolites of catecholamines)¹² at three weeks and six months of age. The three-week examination took place at the same time as an existing screening for inborn errors of metabolism, whereas the six-month screening required a new test. Information regarding the study was distributed to parents at the time of a child's birth. Parents were asked to send urine-saturated filter papers to the screening center at both study time points, although they could choose not to do so. Return of the filter papers to the screening center was considered to indicate consent to participate. Written informed consent for evaluation for possible neuroblastoma was obtained from parents of all children whose screening tests were positive.

A total of 476,654 children were born in the province of Quebec during the study period (49 percent were female; 83 percent were white, 1 percent Native Canadian, 1 percent Asian, 1 percent black, 0.4 percent Hispanic, and 14 percent other or unknown). Parents of 425,838 children (89 percent) voluntarily agreed to participation in the three-week screening, and parents of 350,150 children (73 percent) voluntarily agreed to participation in the six-month screening; overall compliance was 92 percent (3 percent of the parents participated in the six-month but not the three-week screening). If two consecutive samples from filter papers tested positive on gas chromatography–mass spectrometry for homovanillic acid, vanillylmandelic acid, or both, the child was referred to one of four centers in Quebec for uniform neuroblastoma evaluation, staging, treatment, and follow-up, as well as for uniform collection of biologic specimens for testing for various prognostic factors.¹³ Filter-paper specimens from all the children who were screened were frozen with appropriate control specimens with known amounts of catecholamine metabolites for retrospective analysis. The screening urine sample was reanalyzed for any child who was given a diagnosis of neuroblastoma but whose disease had not been detected by the original screening. The study was approved by institutional review boards that had been sanctioned by the U.S. National Institutes of Health.

Control Groups and Ascertainment of Cases of Neuroblastoma and Associated Deaths

Children born during the study period in several geographic areas in which screening was not offered were followed by project investigators in the same manner as those in Quebec to whom screening was offered. The control areas included the province of Ontario, Canada; the states of Minnesota and Florida; and the Greater Delaware Valley, a 31-county area that has one of the largest pediatric cancer registries in the world.¹⁴ Investigators used locally available mechanisms, including provincewide or statewide tumor registries, to identify cases of neuroblastoma and deaths from neuroblastoma. Assistance was provided by the Children's Cancer Group and the Pediatric Oncology Group, which collectively treat 95 percent of all cases of childhood cancer in North America,¹⁵ including cases from all the study and control areas.

Concurrently, cases of neuroblastoma and deaths from neuroblastoma in Quebec, Ontario, and the rest of Canada were tracked independently by Statistics Canada, a Canadian federal agency that manages statistical information, with the use of provincial cancer registries for cases and the Canadian Vital Statistics Data Base for deaths.¹⁶ All death certificates for children who had died by December 31, 1998, after a diagnosis of a solid tumor and who had been born during the five-year study period were examined; further information was obtained when the diagnosis of neuroblastoma was considered questionable by the investigator from Statistics Canada. Separate mortality analyses were then performed with the use of these independently collected data. Investigators

at Statistics Canada had identified every death from neuroblastoma in Quebec that had been found by the project investigators. Similarly, project investigators in Quebec had identified every death noted in the Canadian Vital Statistics Data Base, with one exception: the death of a newborn with the diagnosis of neuroblastoma whose disease was never brought to the attention of clinicians. Thus, it is presumed that the ascertainment of cases was complete. Finally, Statistics Canada used identical ascertainment procedures to collect data on deaths from neuroblastoma in historical cohorts to be used as standards for comparison.

Movement into and out of Quebec during the study period was also carefully tracked. Three children who were born in Quebec subsequently received a diagnosis of neuroblastoma while they were residing in other geographic areas, having moved from Quebec before the diagnosis; neuroblastoma was detected by screening in two of these children, who are still alive, and the third was never screened and subsequently died. In addition, two children were given a diagnosis of neuroblastoma while residing in Quebec but had been born elsewhere: as of this writing, both of these children remain alive. On the basis of previous census data, project investigators had prospectively estimated that the same number of children with neuroblastoma would move into and out of Quebec.¹⁰ For all analyses, we included in the group of children with neuroblastoma in the study cohort and each of the control cohorts all children with neuroblastoma born during the five-year study period who lived in the cohort's geographic area when the disease was diagnosed, irrespective of their place of birth.

Statistical Analysis

For each control group, we obtained the number of deaths from neuroblastoma and the number of person-years at risk according to the year of age. The expected number of deaths among children in each one-year age range in the Quebec cohort was calculated as the number of deaths among children in that age range in the particular control cohort times the ratio of person-years at risk in the screened cohort to person-years at risk in the control cohort. The overall expected number of deaths was calculated as the sum of the age-range-specific values. The standardized mortality ratio was calculated as the ratio of the number of deaths observed in the screened Quebec cohort to the expected number of deaths calculated on the basis of the rate in the control cohort. A minor variation of the methods of Breslow and Day¹⁷ was used in which the statistical variation in the expected number of deaths was taken into account. In most studies analyzing population-based mortality, the control groups are much larger than the case groups, and therefore the statistical variation in the expected number of deaths can be ignored as insubstantial. In our study, as in most population-based studies involving childhood cancer, such variation cannot be ignored, because of the infrequency of the condition under study.

These analytic techniques were applied to three sets of data. The first set included data on the Quebec cohort born between May 1, 1989, and April 30, 1994, and on the four control cohorts, with end points ascertained by the project investigators. For the analyses involving this data set, follow-up continued until eight years of age or until April 30, 2000, whichever was earlier. The second set included data obtained from Statistics Canada for children born during the same period in Quebec and in the rest of Canada. For the analyses involving this data set, follow-up continued until eight years of age or until December 31, 1998, whichever was earlier. The third set included the data, obtained from Statistics Canada, for the original Quebec cohort and for two earlier birth cohorts (one from Quebec and the other from Canada as a whole) born between May 1, 1984, and April 30, 1989 (the five years before the cohort that was offered screening); the retrospective data included cases diagnosed and deaths that occurred through eight years of age or through December 31, 1993, whichever was earlier.

Although the follow-up rate was high (over 95 percent at five years), some children with neuroblastoma were lost to follow-up.

In our analysis, we censored the data at the time of the last contact. Since children with neuroblastoma have a higher risk of dying from neuroblastoma than the general population, we performed a detailed simulation, with a method similar to the stochastic curtailment used in clinical trials, to assess the potential effect of the missing information. Using the available outcome data, we statistically simulated the remaining follow-up — to eight years of age or April 30, 2000, whichever was earlier — of children with neuroblastoma whose data had been censored. The mean simulated standard mortality ratios and 95 percent confidence limits for the comparisons with all four control groups were within 2 percent of those estimated in the original analysis, and the standard deviations differed by less than 2.5 percent. We estimate that follow-up of the Quebec cohort was 99.7 percent complete with respect to mortality from neuroblastoma by eight years of age or April 30, 2000, whichever was earlier; the corresponding estimates for the control cohorts were 98.2 percent in Ontario, 99.9 percent in Minnesota, 98.6 percent in Florida, and 98.3 percent in the Greater Delaware Valley. We conclude that losses to follow-up did not materially affect the results. A technical description of the sensitivity analysis is available as Supplementary Appendix 1 with the full text of this article at <http://www.nejm.org>.

RESULTS

Deaths in the Quebec Cohort

During follow-up of 72 to 132 months, through April 30, 2000, there were 22 deaths from neuroblastoma identified in the Quebec cohort. Three children with stage 4S disease that was diagnosed before the three-week screening died. Two of these children died from rapidly expanding metastases in the liver and respiratory compromise (one child died 9 days after diagnosis, and the other died 1 month after diagnosis); the third child had a tumor with unfavorable biologic features, including an amplified *MYCN* oncogene, and died 7.5 months after diagnosis. Of the remaining 19 children who died from neuroblastoma, all but 1 had been screened, with negative results. For all 18 missed cases, the original filter papers, which had been frozen and stored, were reanalyzed. Only one tested positive for catecholamines in a dilute sample, indicating that neuroblastoma could have been detected by screening. In the other 17 cases, normal catecholamine results were confirmed. Tissue from 17 of the 21 patients whose tumors were evaluated had at least one unfavorable prognostic feature (e.g., amplified *MYCN* oncogene expression, pseudodiploid or tetraploid DNA content, or unfavorable histologic features) (Table 1).

Outcome of Cases Detected by Screening

Overall, there were 43 cases of neuroblastoma in Quebec that were diagnosed by screening.¹⁰ In contrast to the tumors that were missed by screening, almost all the tumors that were detected by screening had favorable biologic features; for example, none of the 43 had an amplified *MYCN* oncogene. All 43 children remain alive as of this writing. However, in one child with stage 2B neuroblastoma that was detected by the screening at six months and who was

TABLE 1. CHARACTERISTICS OF NEUROBLASTOMA IN THE 22 CHILDREN WHO DIED OF THE DISEASE IN THE QUEBEC COHORT.

VARIABLE	CHILDREN WITH VARIABLE no./no. evaluated (%)
Stage of tumor	
4S	3/22 (14)
4	17/22 (77)
3	2/22 (9)
Elevated urinary catecholamines	16/22 (73)
Unfavorable biologic characteristics	
Unfavorable DNA ploidy*	12/21 (57)
Amplified <i>MYCN</i> oncogene	11/19 (58)
Unfavorable histologic findings†	11/11 (100)
At least one of the above	17/21 (81)

*Values include children with tumors with pseudodiploid or tetraploid DNA content.

†Histologic analysis, by the method of Shimada et al., was performed only on the tumors of 11 children in whom the diagnosis of neuroblastoma was made on the basis of a biopsy of the primary tumor or a removed tumor. No histologic analysis was possible in the cases of the 10 children in whom the diagnosis was made on the basis of the examination of the bone marrow and the measurement of urinary catecholamines.

treated with doxorubicin and cyclophosphamide, a secondary leukemia with an abnormality in chromosome 11q23 subsequently developed; that child underwent bone marrow transplantation and is alive but has severe graft-versus-host disease. An additional child whose disease was detected by screening is in a persistent vegetative state as a result of complications of surgery for severe gastrointestinal obstruction and necrosis. The gastrointestinal problems were attributed to adhesions that resulted from the surgery to remove the neuroblastoma seven years earlier.

Mortality from Neuroblastoma in the Screened Quebec Cohort

The 22 deaths among children younger than eight years of age in Quebec represented a cumulative (\pm SE) mortality of 4.78 ± 1.14 per 100,000 children over a nine-year period (Fig. 1). There were similar results in Ontario, Minnesota, Florida, and the Greater Delaware Valley. The risk of mortality due to neuroblastoma for children in Quebec up to eight years of age was not significantly lower than the risk in these control groups (Table 2).

Similarly, standard mortality ratios by December 31, 1998, were determined with the use of data collected by Statistics Canada, through the comparison of the rate in the screened Quebec cohort with the historical standards — rates during the previous five years in Quebec and in all of Canada — as well as

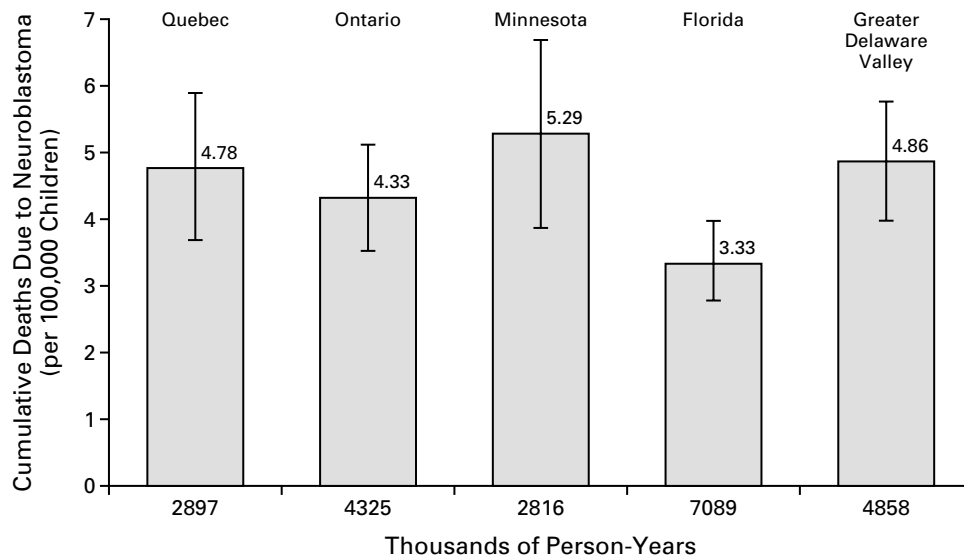


Figure 1. Cumulative Mortality Due to Neuroblastoma among Children Younger Than Eight Years of Age. The I bars represent the SE.

TABLE 2. RATE OF DEATH DUE TO NEUROBLASTOMA BY EIGHT YEARS OF AGE IN THE SCREENED QUEBEC COHORT, AS COMPARED WITH THE RATES IN FOUR UNSCREENED COHORTS.*

CONTROL COHORT	NO. OF DEATHS EXPECTED IN QUEBEC ON THE BASIS OF THE CONTROL COHORT	STANDARDIZED MORTALITY RATIO FOR QUEBEC (95% CI)
Ontario	19.8	1.11 (0.64–1.92)
Minnesota	24.4	0.90 (0.48–1.70)
Florida	15.7	1.40 (0.81–2.41)
Greater Delaware Valley	22.8	0.96 (0.56–1.66)

*There were 22 deaths due to neuroblastoma in the screened Quebec cohort. Data were collected by the project investigators through April 30, 2000. CI denotes confidence interval.

TABLE 3. RATE OF DEATH DUE TO NEUROBLASTOMA BY EIGHT YEARS OF AGE IN THE SCREENED QUEBEC COHORT, AS COMPARED WITH THE RATES IN UNSCREENED CANADIAN COHORTS.*

CONTROL COHORT	NO. OF DEATHS EXPECTED IN QUEBEC ON THE BASIS OF THE CONTROL COHORT	STANDARDIZED MORTALITY RATIO FOR QUEBEC (95% CI)
Historical cohorts		
Quebec	22.5	0.98 (0.54–1.77)
Canada	21.2	1.04 (0.64–1.69)
Concurrent cohort		
Canada excluding Quebec	15.8	1.39 (0.85–2.30)

*There were 22 deaths from neuroblastoma in the screened cohort. Data for the screened and concurrent cohorts were collected through December 31, 1998. Data for the historical cohorts are for children born between May 1, 1984, and April 30, 1989, with follow-up through 1993. All data were collected by Statistics Canada. CI denotes confidence interval.

with the concurrent rate in the rest of Canada (excluding Quebec) (Table 3). When the screened cohort was compared with the historical control cohorts, no reduction in mortality due to neuroblastoma was found. The standardized mortality ratio for Quebec as compared with the concurrent cohort in the rest of Canada was 1.39 (95 percent confidence interval, 0.85 to 2.30).

DISCUSSION

The concept of lowering mortality by the detection of preclinical neuroblastoma is an appealing one. In pioneering work, Japanese investigators demonstrated that neuroblastoma could be detected by screening for urinary catecholamines at six months of age and offered evidence of improvement in the survival of children with neuroblastoma.^{4,5} However, several

methodologic limitations in these and other related studies precluded definitive conclusions. None of the early studies used population-based approaches for screening for neuroblastoma, and none used concurrent control groups.^{4,5} Subsequent studies performed in relatively small populations found no diminution in the incidence of late-stage disease, the incidence of disease with unfavorable biologic features, or mortality.¹⁸⁻²¹ Once quantitative methods for measuring metabolites of catecholamine had been implemented, the rate of diagnosis of neuroblastoma increased in Japan²²; if cases with good prognoses were preferentially detected, survival might appear to be improved, even if the number of deaths was unchanged.

The purpose of our study was to test the hypothesis that screening infants for neuroblastoma could reduce mortality due to this disease. The most sensitive and specific methods for measuring catecholamine metabolites were implemented, with screening offered at two distinct times.⁸ Reanalyses of all filter papers from 18 children in Quebec with negative screening tests who later received a diagnosis of neuroblastoma confirmed that all but one case would not have been detected by measurement of catecholamine metabolites at six months of age or younger.

A randomized, controlled trial is considered by some to be the ideal approach to evaluating screening for neuroblastoma.²³ We postulated, however, that the introduction of a new screening program and the associated publicity might have a "halo effect" beyond the screened group^{10,24}; it would thus be difficult in a randomized trial to maintain an appropriate control group that was unaffected by the intervention.²⁴ We instead conducted a prospective population-based study, comparing a screened population in Quebec with concurrent control populations in several geographic areas in North America. The observation that mortality from neuroblastoma in all our control areas, as well as in Quebec in the years before the screening program, was similar to that in the screened cohort^{2,16} confirmed that there is little difference in the outcome of neuroblastoma throughout North America. Because neuroblastoma occurs almost exclusively in the first several years of life, we were able to identify virtually all cases of neuroblastoma and associated deaths. Such complete ascertainment cannot be achieved without much longer follow-up in most studies of cancer in adults.

The mortality due to neuroblastoma documented in Quebec was no lower, and was indeed somewhat higher, than that in the collective control groups. Given the small number of deaths caused by this relatively rare condition, the confidence intervals around the estimated risk of death are relatively wide, and a small improvement in mortality cannot be ruled out. Even if there were a small improvement, however, the mas-

sive cost that would be involved in building an infrastructure to collect urine from children throughout North America²⁵ could not be justified for such a small gain. It is more likely that screening has no effect on mortality due to neuroblastoma. This study did not evaluate whether screening for neuroblastoma at a later age — i.e., at 12 months or older — might be more effective.²⁶

Our study has additional implications. Our results add further weight to a large body of evidence suggesting that neuroblastoma represents at least two distinct clinical and biologic entities.^{27,28} Disease with a favorable prognosis is detectable by screening but is associated with a very high rate of spontaneous regression or maturation of neuroblastomas into benign ganglioneuromas. Preliminary biologic results from our study and others suggest that very few cases of neuroblastoma that are detected by screening have unfavorable biologic features.^{13,20} Thus, there is a possibility of causing harm by treating cases detected by screening that would otherwise have a benign course. On the other hand, disease with an unfavorable prognosis is rarely detectable by screening and appears not to be affected by this public health intervention.

Our study may have practical implications for the care of infants with clinically detected neuroblastoma. Yamamoto and colleagues have now defined criteria according to which neuroblastomas detected by screening may simply undergo observation without incurring any untoward risks.²⁹ These criteria include the identification of small masses on radiography, with no invasion of the intraspinal canal or infiltration around the great vessels; relatively moderate catecholamine secretion; and parental consent. We hypothesize that a substantial portion of infants in whom neuroblastoma is diagnosed clinically at less than six months of age can also be observed for potential regression of the tumor rather than undergo major surgery. In countries such as Japan where screening for neuroblastoma is mandatory, this policy should be reconsidered. A study is needed to determine whether such an approach will help lower morbidity in infants with this disease. Screening infants for neuroblastoma does not appear to reduce population-based mortality.

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