A population-based study of the usefulness of screening for neuroblastoma

William G Woods, Mendel Tuchman, Leslie L Robison, Mark Bernstein, Jean-Marie Leclerc, Linda C Brisson, Josee Brossard, Gerry Hill, Jonathan Shuster, Russell Luepker, Timothy Byrne, Sheila Weitzman, Greta Bunin, Bernard Lemieux

Summary

Background Neuroblastoma has many characteristics which suggest that preclinical detection might improve outcome. The Quebec Neuroblastoma Screening Project was initiated to determine whether mass screening could reduce mortality in a large cohort of infants. As an early endpoint, we report whether screening could reduce the incidence of poor-prognosis neuroblastoma in children with advanced-stage disease over 1 year of age.

Methods All 476 603 children born in the province of Quebec during the 5-year period of May 1, 1989, to April 30, 1994, were eligible for urinary assay of homovanillic acid and vanillylmandelic acid at 3 weeks and 6 months of age. Children with a positive screen were referred to one of four paediatric cancer centres in the province for uniform evaluation and treatment if necessary. Standardised incidence ratios (SIRs) were calculated for neuroblastoma in the province and two similar population-based controls, the state of Minnesota and the province of Ontario, during the same period of time and with similar ascertainment procedures.

Findings Compliance with screening in Quebec province was 91% at 3 weeks (n=425 816) and 74% at 6 months (n=349 706). Through July 31, 1995, with a follow-up of the birth cohort of 15–75 months, 118 cases of neuroblastoma were diagnosed, 43 detected preclinically by screening, 20 detected clinically before screening at 3 weeks of age, and 55 detected clinically after 3 weeks of age having normal screens (52) or never screened (3). Retrospective analysis of stored samples confirmed that 49 of 52 patients missed by screening had levels of catecholamine metabolites that were too low to be detected at 6 months or earlier. Based on US Surveillance, Epidemiology and End Results data, 54·5 cases of neuroblastoma would have been expected in Quebec province during the study period, for an SIR of 2·17 (95% CI 1·79–2·57, p<0·0001). For the two control groups, 43 and 80 cases of neuroblastoma were detected, respectively, compared with 37·9 and 85·4 expected, overall SIR 1·00 (not significant). SIRs for Quebec province by age at diagnosis in yearly intervals show a marked increased incidence under 1 year of age (SIR 2·85, 2·26–3·50), with no reduction in incidence in subsequent years. Limiting analysis to only patients diagnosed over 1 year of age with advanced-stage disease, 22 cases were detected in Quebec province versus 14·4 expected (SIR 1·52, 0·95–2·23). Data in the two control groups show no significant increase or decrease in any-stage disease in children under or over the age of 1 year, except for an increase in early-stage disease in Minnesota children over 1 year: 10 versus 3·8 expected (SIR 2·67, 1·27–4·58).

Interpretation Screening for neuroblastoma increases the incidence in infants without decreasing the incidence of unfavourable advanced-stage disease in older children. It is unlikely that screening for neuroblastoma in infants will reduce mortality for this disease

Lancet 1996; **348:** 1682–87

See Commentary page 1672

Introduction

Neuroblastoma is the most common solid tumour of children aged under 5, cumulatively affecting about one in 7000 individuals.[1,2] Despite major advances in the treatment of other childhood cancers, the overall outcome for neuroblastoma has not changed in the past 15–20 years.[2]

The potential that neuroblastoma could be detected by screening for catecholamine metabolites has been pioneered by several Japanese investigators, who documented that neuroblastoma can be diagnosed preclinically with almost uniformly favourable survival.[3,4] Neuroblastoma screening was instituted nationwide in Japan in 1985. However, several methodological limitations, including lack of well-documented and well-controlled population-based studies with adequate ascertainment, preclude a conclusion that preclinical detection of this disease will reduce mortality.[5,6] The Quebec Neuroblastoma Screening Project was started to determine whether screening a large birth cohort of infants for neuroblastoma could reduce population-based incidence of advanced disease or mortality. With use of the infrastructure of the Quebec Network for Genetic Medicine,[7] screening for neuroblastoma was instituted in a 5-year birth cohort. Province-wide incidence and mortality results are being compared to several population-based control groups in North America in which infants were not offered screening.[8] Here we document whether neuroblastoma screening can reduce the incidence of unfavourable, advanced stage disease in older children.

University of Minnesota, Minneapolis, Minnesota, USA (Prof W G Woods MD, Prof M Tuchman MD, Prof L L Robison MD, Prof R Luepker MD, T Byrne MS)**; Montréal Children's Hospital, Montréal, Quebéc, Canada** (M Bernstein MD)**; Ste-Justine Hôpital, Montréal** (J-M Leclerc MD)**; Centre Hospitalier l'Université Laval, Ste-Foy, Quebéc** (L C Brisson MD)**; Centre Hospitalier l'Université Sherbrooke, Sherbrooke, Quebéc** (J Brossard MD, Prof B Lemieux MD)**; Bureau of Chronic Disease Epidemiology, Ottawa, Ontario** (G Hill MBBS)**; Department of Statistics, University of Florida, Gainesville, Florida** (Prof J Shuster PhD)**; Hospital for Sick Children, Toronto, Ontario** (Prof S Weitzman MD)**; and Children's Hospital of Philadelphia, Philadelphia, Pennsylvania** (G Bunin PhD)

Correspondence to: Prof William G Woods, South Carolina Cancer Center, Richland Memorial Hospital, 7 Richland Medical Park, Columbia, SC 29203, USA

Methods

Quebec Neuroblastoma Screening Project

Specific aspects of the study design have been published.[8,9] Parents of infants born in the province of Quebec during a 5-year period (May 1, 1989, to April 30, 1994) were offered, after informed consent, the opportunity to have urine samples from their infants tested at 3 weeks and 6 months of age for elevated catecholamine metabolites (vanillylmandelic and homovanillic acids). Parents collected urine by blotting filter papers against wet diapers (nappies), and drying and mailing them to the project in Sherbrooke. The first screen at 3 weeks of age was done on the sample used for screening for metabolic diseases,[9] with a compliance rate of 91%. The second screen at 6 months was a new test. Filter papers were provided to the parents at birth and multiple reminders were given;[8,10] compliance with the second screen was 74%.

At the screening centre, thin-layer chromatography (TLC) for catecholamine metabolites was done.[8,9] Parents of infants with insufficient or contaminated samples were contacted for repeat testing. Samples with borderline or positive TLC results (figure 1) were sent to Minneapolis for gas-chromatography/mass-spectrometry (GCMS) assay.[8] Parents of children with abnormal results were contacted for second filter papers for GCMS. Patients with positive second analyses were referred to one of four Quebec province centres for evaluation.[8] Filter paper specimens from all children screened were frozen with appropriate controls for retrospective analyses from every patient diagnosed with neuroblastoma and missed by screening.

Ascertainment of neuroblastoma in Quebec

Children with neuroblastoma in Quebec province were ascertained by several methods.[2] Traditionally, over 90% of all patients with neuroblastoma diagnosed in this province have been referred to one of the four provincial paediatric cancer centres. Close contact was established between study investigators and Canadian medical centres outside the province where patients may have received care.

All Quebec province patients diagnosed with neuroblastoma underwent uniform staging by the Evans', Pediatric Oncology Group, and International Neuroblastoma Staging System (INSS).[11] Four study investigators routinely reviewed each staging, with difficult cases staged by consensus. Samples for specific indices known to have prognostic importance in neuroblastoma, including N-*myc* gene copy-number, DNA ploidy, *trk* gene expression, serum ferritin, catecholamine metabolites, and histology, were collected in over 98% of all children diagnosed. Patients with neuroblastoma were subsequently treated based on age, stage, and biological features on specific protocols open during the study period (Pediatric Oncology Group studies 8105, 8741/2/3, 8844, 9140, 9243/4, 9248, and 9340/1/2).

Control groups

Two population-based non-screened control groups were followed up during the same 5-year period, with examination of neuroblastoma indices: (1) the state of Minnesota, with Children's Cancer Group data and the population-based, pathology-based Cancer Surveillance System;[12] and (2) the

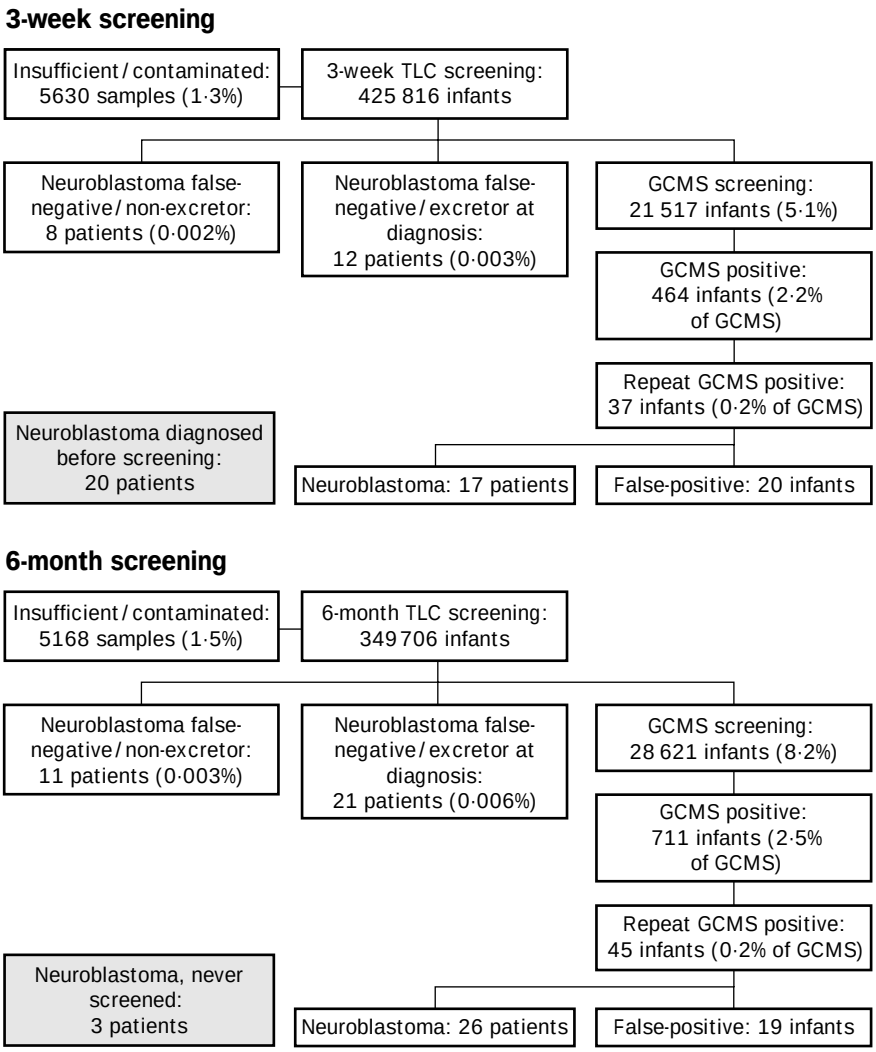

Figure 1: **Neuroblastoma screening logistics at 3 weeks and 6 months of age**

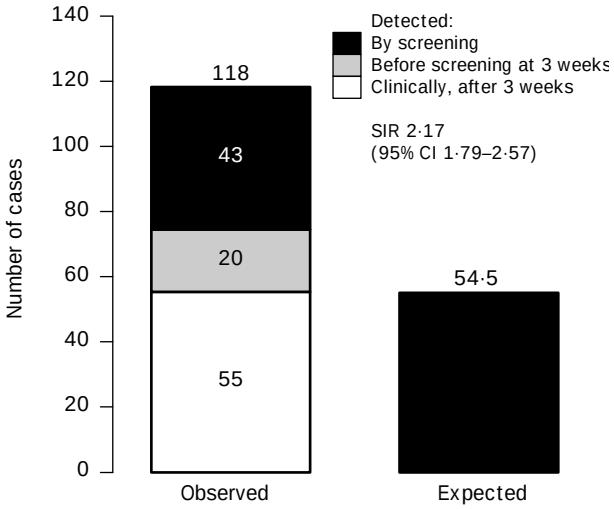

Figure 2: **SIR of neuroblastoma incidence in province of Quebec for 5-year screened cohort versus US SEER data**

province of Ontario, because of the ability to ascertain cases through the Pediatric Oncology Group of Ontario[13] and its close proximity to Quebec province. Furthermore, the incidence and mortality of neuroblastoma in Quebec province was previously compared with data from the Greater Delaware Valley, the largest population-based paediatric tumour registry in North America,[14] for a 10-year period (1977–86), with similar outcomes found (incidence $11{\cdot}3/10^6$ per year in Quebec *vs* $10{\cdot}6/10^6$ per year in Delaware Valley).[2] All control patients were staged by the three systems noted above and appropriate data gathered.

Statistical and other analyses

To evaluate the occurrence of neuroblastoma within the study populations, the person-years of observation were compiled for subgroups defined by age. Using 1-year age-specific incidence rates from the US Surveillance, Epidemiology and End Results (SEER) programme,[15] we calculated standardised incidence ratios (SIRs) and corresponding 95% CIs for Quebec, Minnesota, and Ontario.[16] SIRs were analysed according to Breslow and Day. SEER incidence rates for whites only (overall $9{\cdot}7/10^6$ per year, similar to other worldwide rates among whites[17]) were used, since greater than 95% of all three populations were white. Stage-specific incidence rates from the Delaware Valley paediatric tumour registry were used for calculation of SIRs within age-specific and stage-specific subgroups because SEER does not collect data on neuroblastoma staging.

Quebec, Minnesota, and Ontario patients were recorded as having neuroblastoma if they lived in the respective area when they were diagnosed with the disease and were born between May 1, 1989, and April 30, 1994, irrespective of place of birth. In-migration and out-migration were expected to be low in Quebec province based on previous census data from the province, with only three cases of neuroblastoma expected to emigrate out and two additional cases expected by immigration during the study period (G Dougherty, Montcare Children's Hospital, McGill University, Montreal). In reality, three patients were diagnosed having emigrated from the area after birth (two detected by screening, one never screened), and no patients were diagnosed while resident there, having been born elsewhere. These three patients were not included in the incidence analysis.

Staging was compared between Quebec, Minnesota, and Ontario based on concurrent ascertainment of cases, with data tabulated by the INSS. As an additional control, incidence of Evans' early (I, II, IVS) and advanced (III, IV) disease in patients under and over the age of 1 was determined for the three study groups and compared with updated, previously acquired and reported Delaware Valley data, obtained at a time when only Evans' staging was used.[2]

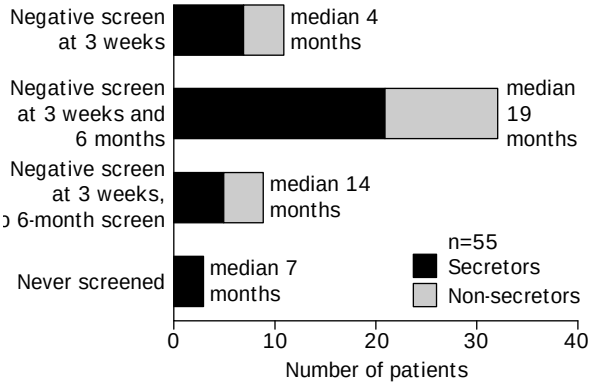

Figure 3: **Cases of neuroblastoma diagnosed in Quebec cohort after 3 weeks of age and missed by screening or never screened**

Results

Cases of neuroblastoma diagnosed in Quebec

Up to July 31, 1995, with a follow-up of 15–75 months, there were 118 cases of neuroblastoma diagnosed among the Quebec province birth cohort (figure 2). 43 patients were detected preclinically, 17 at the 3-week screen and 26 at the 6-month screen. The patients referred to the four Quebec medical centres after positive screenings are shown in figure 1. The selectivity of both the 3-week and 6-month screens was over 99·99%. The overall positive predictive value of the screening approach, including the repeat test, was 52% (43 of 82). INSS neuroblastoma staging of Quebec province cases diagnosed through screening is summarised in table 1. All patients detected by screening are alive and disease-free.

During the study period, 55 patients were detected clinically after 3 weeks of age, having been undetected by screening (52) or never screened (3) (figure 3). Only 3 patients in the entire cohort had positive tests by GCMS retrospective analysis of the 6-month samples. Two children were diagnosed at 7 and 8 months with localised tumours and are well. One child presented clinically at 53 months with stage 4 neuroblastoma who, in retrospect, had an increased homovanillic acid at the 6-month screen. Review of videotaped original TLC analysis confirmed a normal result, probably after submission of a dilute urine sample. All 49 other children missed by screening could clearly not have been detected because their catecholamines were normal at screening. Overall sensitivity of the screening approach was 45%.

An additional 20 neuroblastoma patients were detected clinically before 3 weeks of age. All had raised vanillylmandelic acids and seven actually had urines

INSS stage	Cases diagnosed before screening at 3 weeks of age	Cases diagnosed through screening	Cases missed by screening or never screened	Total*
1	10	10	14	34
2A	1	0	2	3
2B	0	11	7	18
4S	6	8	3	17
3	1	6	5	12
4	2	8	24	34
Total	20	43	55	118

*See figure 4.

Table 1: **INSS staging of 118 neuroblastoma cases in Quebec for 5-year screened cohort**

Age at diagnosis (months)	Quebec	Minnesota controls	Ontario controls
0–11			
Person-years	476 172	331 480	747 996
Observed	81	17	40
Expected	28·48	19·82	44·73
SIR	2·85	0·86	0·89
95% CI	2·26–3·50	0·50–1·31	0·64–1·19
12–33			
Person-years	448 248	311 864	703 170
Observed	20	13	24
Expected	12·69	8·83	19·90
SIR	1·58	1·47	1·21
95% CI	0·96–2·34	0·78–2·38	0·77–1·74
24–35			
Person-years	358 234	143 797	558 594
Observed	8	8	7
Expected	8·31	5·77	12·96
SIR	0·96	1·39	0·54
95% CI	0·41–1·74	0·59–2·51	0·21–1·01
36–47			
Person-years	262 540	183 087	408 088
Observed	5	4	5
Expected	2·99	2·09	4·65
SIR	1·67	1·92	1·08
95% CI	0·53–3·46	0·50–4·25	0·34–2·22
48–59			
Person-years	164 885	116 261	256 676
Observed	2	1	4
Expected	1·73	1·22	2·70
SIR	1·16	0·82	1·48
95% CI	0·11–3·31	0·00–3·21	0·39–3·30
60–71			
Person-years	45 291	32 606	71 219
Observed	2	0	0
Expected	0·30	0·22	0·47
SIR	6·69	. .	. .
95% CI	0·63–19·18	. .	. .
Total			
Births	476 603	331 425	748 532
Person-years	1 755 460	1 119 095	2 745 743
Observed	118	43	80
Expected	54·50	37·94	85·41
SIR	2·17	1·13	0·93
95% CI	1·79–2·57	0·82–1·50	0·74–1·14

Table 2: **SIRs for neuroblastoma at 1-year age intervals versus US SEER data**

submitted to the screening programme when they were detected clinically. 13 of the patients were found by routine neonatal examinations, one was detected as an incidental finding at surgery for other reasons, and six were detected by chest radiography or ultrasounds done for other reasons, including two performed prenatally.

Incidence of neuroblastoma in Quebec and control groups

Based on SEER data, 54·5 cases of neuroblastoma were expected to be diagnosed in Quebec province children born during the cohort period, with 118 cases observed thus far. The SIR is 2·17 (95% CI 1·79–2·57, $p<0·0001$, figure 2 and table 2). Table 2 lists incidence data for this province and the two control groups. The SIR for the combined control groups is 1·00 with neither group showing statistically significant changes.

When we examined incidence by age at diagnosis in yearly intervals (table 2), the observed to expected ratio of cases diagnosed with neuroblastoma under 1 year of age in Quebec province was significantly higher than that expected (SIR 2·85, 95% CI 2·26–3·50). For each of the subsequent yearly periods there was no significant decrease in incidence (table 2). Overall SIR for ages 1–6 was 1·42 (1·00–1·92). No statistically significant increased or decreased incidences were seen in either Minnesota or Ontario for any of the six age-groups studied.

Neuroblastoma staging in the Quebec and control cohorts

INSS results are compared for Quebec, Minnesota, and Ontario groups in figure 4. The numbers of patients in the control groups were "normalised" to the Quebec province population by comparing number of births for the 5-year cohorts. For example, Quebec to Minnesota births were 476 603 to 331 425, or 1·44. The actual numbers of INSS stage 1 tumours in Minnesota was 11. The number normalised to the Quebec population was $11 \times 1·44$, or 15·8. The number of Quebec province patients diagnosed with early-stage disease, especially stage 1, was far in excess of that in the control groups. However, no concomitant decrease was noted in the more advanced stages 3 and 4, as would have been expected had preclinical detection of neuroblastoma reduced the incidence of late-stage disease. In fact, the number of cases with stage 4 disease diagnosed in Quebec province (34) is much greater than that seen in the normalised control groups (25·9 and 15·9 in Minnesota and Ontario, respectively), with only a portion of the excess in Quebec diagnosed in children under 1 year by screening (table 1).

Finally, the SIRs of early and advanced Evans' stage neuroblastoma in infants and older children were calculated with Greater Delaware Valley data (table 3). The SIR for Quebec province cohort is high compared with Delaware Valley (2·39, 1·98–2·84), with Minnesota and Ontario showing no significant increases or decreases (table 3). 45 advanced-stage cases were diagnosed during the study period in Quebec province, versus 26·0 expected (SIR 1·73, 1·26–2·28). For the critical group with advanced-stage disease diagnosed over 1 year of age, no decrease was observed, with 22 Quebec cases detected versus 14·4 expected (SIR 1·52, 0·95–2·23). By contrast, late advanced neuroblastoma incidence in the two control groups was similar to that in Quebec province. Furthermore, the occurrence of late advanced disease in Quebec before screening, both 1977–86[2] and 1987–89 (overall 77 cases observed *vs* 49·9 expected, SIR 1·56, 1·23–1·92) was identical to that observed in the screened population.

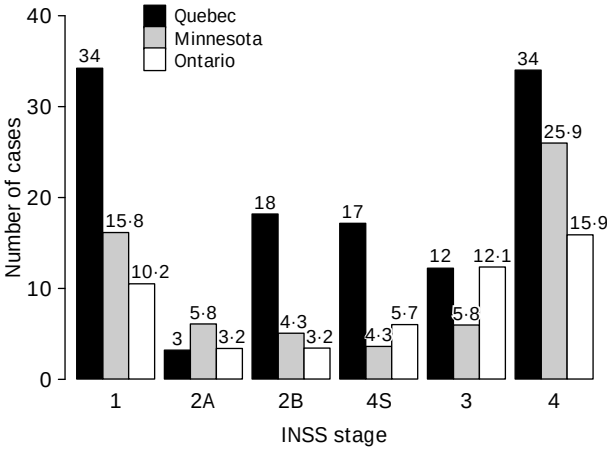

Figure 4: **INSS staging of neuroblastoma cases comparing Quebec with Minnesota and Ontario**
Control groups normalised to birth size of Quebec based on 5-year birth cohorts.

Discussion

Neuroblastoma has several features that at first glance suggest that preclinical detection would reduce mortality. The disease has been hypothesised to be an embryonal neoplasm that presents with decreasing frequency from birth to age 5. When infants are diagnosed with the disease, the tumour is often localised, exhibits favourable biological characteristics, and has an excellent prognosis, even when diagnosed in advanced or "special" (4S) stage. On the other hand, children diagnosed over the age of 1 have a poor outcome, most presenting with widely disseminated disease and resistance to aggressive therapy, including bone-marrow transplantation.[18] Catecholamine metabolites are excreted in the urine of children with neuroblastoma and easily detected.[8,9] Unfortunately, the overall outcome for neuroblastoma has lagged behind that of other common paediatric neoplasms.[2,18]

Introduction of screening in Quebec province profoundly changed the natural history of the disease, resulting in more than a two-fold increase in incidence. The increase was largest for infants aged under 1 year. Even if we ignore the 3-week screen, the incidence of neuroblastoma in the Quebec cohort was dramatically increased. This would have been desirable had the incidence of neuroblastoma decreased in older children, but such was not the case. SIRs from 1 to 6 years showed an increase in the incidence, with no decreases noted in advanced disease at any age, overall disease in children over 1, or advanced disease in patients older than 1 in whom prognosis can be expected to be poor (tables 2 and 3, figures 2 and 4). Although we cannot say that neuroblastoma screening may not help an occasional patient, such as the one child missed by screening who was diagnosed with stage 4 disease at 53 months, the confidence intervals we calculated suggest that at most a 5% reduction in older poor-prognosis neuroblastoma could be detected (table 3). Overall changes noted in Quebec province were not seen in the two concurrent population-based control cohorts, Minnesota and Ontario, which has similar neuroblastoma ascertainment procedures and staging review. The incidence ratios for late-stage disease at over 1 year of age were elevated in Quebec before and after screening was initiated. Similar increases were present in the Minnesota and Ontario populations, suggesting that the age-specific and stage-specific incidence rates derived from the Greater Delaware Valley Tumour Registry, may understimate the true incidence within this specific subgroup.

Compared with our approach, what might a randomised controlled trial have shown? The similarity of neuroblastoma in North America prescreening makes it highly unlikely that use of the geographical controls introduced significant bias. Furthermore, the "halo" effect noted below would have involved both control and screened patients in a randomised population, hence confounding any results. We were testing an entire screening "approach", not just the introduction of a screening test itself. As an additional control, annual incidence in Quebec province during the screening period, about $66/10^6$ for the 0–4 age group as calculated from our data, is 2·4-fold higher than in the province before screening ($28/10^6$).[2]

Neuroblastoma may represent at least two distinct clinical-biological entities.[19,20] One, favourable disease, probably congenital, is associated with young age and early stage at diagnosis, triploid karyotypes, no chromosome 1p abnormalities or N-*myc* amplification, more mature catecholamine synthesis and excretion, and excellent clinical outcome despite no or minimum therapy. Favourable neuroblastoma appears to be easily detected through screening for catecholamide metabolites, both in Japan[3,4] and in Quebec province. The second, unfavourable neuroblastoma, presents at an older age, generally with advanced stage, pseudodiploid karyotypes and 1p deletions, N-*myc* amplification, less mature catecholamine synthesis and excretion, and poor outcome. Our data here and that suggested in smaller studies in Japan[21,22] document that screening for neuroblastoma at or before 6 months of age does not reduce the incidence of unfavourable neuroblastoma. Overall results of biological features, which will be reported elsewhere, confirm that characteristics of neuroblastomas detected by screening, or clinically detected before 1 year of age, are generally favourable, while older children detected clinically generally have neuroblastomas with unfavourable biology.[23]

Our results demonstrate a striking "halo" effect from the screening programme in which the overall incidence of neuroblastoma was increased, even if one excludes patients detected by screening (figure 2). Multiple public-relations and public-health methods aimed at improving compliance with screening in Quebec province were implemented during the screening period. Increased awareness of neuroblastoma in the entire province by health-care providers apparently led to more cases diagnosed than would have been otherwise, especially

Stage	Quebec			Minnesota controls			Ontario controls		
	<1 year	⩾1 year	Total	<1 year	⩾1 year	Total	<1 year	⩾1 year	Total
Early stage (I, II, IVS)									
Observed	58	15	73	11	10	21	25	10	35
Expected	19·12	5·37	24·49	13·36	3·75	17·11	30·47	8·42	38·89
O/E	3·03	2·80	2·98	0·82	2·67	1·23	0·82	1·19	0·90
95% CI	2·30–3·86	1·56–4·39	2·34–3·70	0·41–1·38	1·27–4·58	0·76–1·81	0·53–1·17	0·57–2·04	0·63–1·22
Advanced stage (III, IV)									
Observed	23	22	45	6	16	22	15	30	45
Expected	11·53	14·44	25·97	8·05	10·08	18·13	18·37	22·67	41·04
O/E	2·00	1·52	1·73	0·76	1·59	1·21	0·82	1·32	1·10
95% CI	1·26–2·89	0·95–2·23	1·26–2·28	0·27–1·46	0·91–2·46	0·76–1·77	0·46–1·28	0·89–1·84	0·80–1·44
All stages									
Observed	81	37	118	17	26	43	40	40	80
Expected	30·65	18·78	49·43	21·41	13·83	35·24	48·84	31·09	79·93
O/E	2·64	1·97	2·39	0·79	1·88	1·22	0·82	1·29	1·00
95% CI	2·10–3·25	1·39–2·66	1·98–2·84	0·46–1·22	1·23–2·67	0·88–1·61	0·59–1·09	0·92–1·72	0·79–1·23

Table 3: **SIRs of early and advanced Evans' stage neuroblastoma versus Greater Delaware Valley data**

in the neonatal period. However, there was also an increase in cases diagnosed over age 1 year (SIR 1·42, 95% CI 1·00–1·92, with SEER controls). Others have hypothesised a similar reason for discrepant neuroblastoma incidences in various developed countries.[24] Theses effects raise the issue of whether children who are diagnosed with favourable neuroblastoma, especially at an early age, need any treatment for their "disease".[23,25] Favourable neuroblastomas rarely, if ever, evolve into unfavourable disease.[26]

Furthermore, quantitation of regressing neuroblastomas[5] was impossible before our project. There has also been the suggestion of an increase in neuroblastoma incidence over the past 50 years.[27,28] We believe that a substantial portion of this increase may be due to better clinical detection of disease destined to regress.

Using state-of-the-art methodology and a compliance rate similar to that in Japan, we found that most children with neuroblastoma will not be detected by the examination of their urine for vanillylmandelic and homovanillic acids, up to 6 months of age, including children diagnosed with neuroblastoma over 1 year who do poorly. Although it has been assumed that all neuroblastomas are present in utero, this may not be the case. Even if neuroblastomas are all embryonal, many do not continuously excrete catecholamines, at least in sufficient quantities to be sure of detection.

Our results differ fom those reported in Japan,[3,4] except for studies in which attempts were made to examine population-based, rather than hospital-based, data.[21–23] Several other explanations may explain this discrepancy.[5,6] Earlier studies were done at a time when survival for neuroblastoma in Japan was inferior to that in North America and Europe. Therapeutic improvements in the past decade may have changed mortality. Screening studies in Japan have used retrospective controls. Finally, ascertainment of neuroblastoma cases and deaths has not been rigorous. For example, virtually no study has mentioned the occurence of neuroblastoma before 6 months of age.

The mortality assessment in the Quebec Project awaits longer follow-up and will give the definitive answer to the effectiveness of screening infants for neuroblastoma. However, the incidence data reported here support the conclusion that screening for this neoplasm in infants will not reduce mortality. Widespread screening for neuroblastoma at or before the age of 6 months, and perhaps even at later ages,[29] therefore should not be adopted anywhere in the world.

Without the cooperation of the population of Quebec, this study would have been impossible. We thank the data managers at the four Quebec medical centres, Aline Blais, Patricia Campion, Doreen Dupuis, and Louise Renaud, for gathering data and biological samples; and Anne Feltis in Ontario who performed a similar role. We also thank the project oversite committee, John Potter, Garrett Brodeur, Harvey Levy, and Robert Castleberry, for helpful criticisms and suggestions throughout.

This study was supported in part by grant CA 46907 from the US National Institutes of Health, the Quebec Network for Genetic Medicine, Montreal, and the National Cancer Institute of Canada (grant #2691).

References

1 Young JL, Ries LG, Silverberg E, et al. Cancer incidence, survival and mortality in children under 15 years of age. *Cancer* 1986; **58:** 598–602.

2 Bernstein ML, Leclerc JM, Bunin G, et al. A population-based study of neuroblastoma incidence, survival and mortality in North America. *J Clin Oncol* 1992; **10:** 323–29.

3 Sawada T, Nakata T, Takasugi N, et al. Mass screening for neuroblastoma in infants in Japan. *Lancet* 1984; ii: 271–73.

4 Nishi M, Miyake H, Takeda T, et al. Effects of the mass screening of neuroblastoma in Sapporo City. *Cancer* 1987; **60:** 433–36.

5 Murphy SB, Cohn SL, Craft AW, et al. Do children benefit from mass screening for neuroblastoma? Consensus statement from the American Cancer Society Workshop on Neuroblastoma Screening. *Lancet* 1991; **337:** 344–46.

6 Woods WG. Screening for neuroblastoma in infants: more questions than answers. *Screening* 1992; **1:** 273–79.

7 Lemieux B, Auray-Blais C, Giguere R, Shapcott D, Tuchman M, Woods W. Quebec urinary screening program 1: a service to the population, 2: a new perspective. In: Therrell TL, ed. Advances in neonatal screening. Elsevier Science Publishers, 1987: 209–10.

8 Tuchman M, Lemieux B, Auray-Blais C, et al. Screening for neuroblastoma at 3 weeks of age: methods and preliminary results from the Quebec Neuroblastoma Screening Project. *Pediatrics* 1990; **86:** 765–73.

9 Lemieux B, Auray-Blais C, Campion P, Giguere R. Thin layer chromatography of homovanillic and vanillylmandelic acids applicable to a large scale neuroblastoma screening program. In: Schmidt BJ, Diament AJ, Loghin-Grosso NS, eds. Current trends in infant screening. Amsterdam: Excerpta Medica, International Cong Ser 848. 1989: 401–05.

10 Campion P, Dupuis DL. Neuroblastoma screening. *Canadian Nurse* 1991; **87:** 17–19.

11 Brodeur GM, Pritchard J, Berthold F, et al. Revisions of the international criteria for neuroblastoma diagnosis, staging and response to treatment. *J Clin Oncol* 1993; **11:** 1466–77.

12 Bender A, MacDonald KL. The Minnesota Cancer Surveillance System: a summary of 1988 data. *Minn Dept Health Disease Control Newsletter* 1991; **19:** 33–39.

13 Greenberg MC, Greenberg C. The Report of the Provincial Pediatric Oncology Working Group. Toronto: Ontario Ministry of Health Publication, 1994.

14 Kramer S, Meadows AT, Jarrett P, Evans AE. Incidence of childhood cancer: experience of a decade in a population-based registry. *JNCI* 1983; **70:** 49–55.

15 Gurney JC, Severson RK, Davis S, Robison LL. Incidence of cancer in children in the United States: sex, race and 1-year age-specific rates by histologic type. *Cancer* 1995; **75:** 2186–95.

16 Vandenbroucke JB. A shortcut method for calculating 95% confidence interval of the standardized mortality ratio. *Am J Epidemiol* 1982; **115:** 303–04.

17 Stiller CA, Parkin DM. International variations in the incidence of neuroblastoma. *Int J Cancer* 1992; **52:** 538–43.

18 Philip T, Zucker JM, Bernard JL, et al. Improved survival at 2 and 5 years in the LMCE-1 unselected group of 72 children with stage 4 neuroblastoma older than 1 year of age at diagnosis: is cure possible in a small subgroup? *J Clin Oncol* 1991; **9:** 1037–44.

19 Woods WG, Lemieux B, Tuchman M. Neuroblastoma represents distinct clinical-biologic entities: a review and perspective from the Quebec Neuroblastoma Screening Project. *Pediatrics* 1992; **89:** 114–18.

20 Brodeur GM, Nakagawara A. Molecular basis of clinical heterogeneity in neuroblastoma. *Am J Pediatr Hematol-Oncol* 1992; **14:** 111–16.

21 Bessho F, Hashizume K, Nakajo T, Kamoshita S. Mass screening in Japan increased the detection of infants with neuroblastoma without a decrease in cases in older children. *J Pediatr* 1991; **119:** 237–41.

22 Yamamoto K, Hayashi Y, Hanada R, et al. Mass screening and age-specific incidence of neuroblastoma in Saitama Prefecture, Japan. *J Clin Oncol* 1995; **13:** 2033–38.

23 Kaneko Y, Kanda N, Maseki N, et al. Current urinary mass screening for catecholamine metabolites at 6 months of age may be detecting only a small portion of high risk neuroblastomas: a chromosome and N-*myc* amplification study. *J Clin Oncol* 1990; **8:** 2005–13.

24 Parker L. SENSE: Study for the Evaluation of Neuroblastoma Screening in Europe. Abstracts from the fourth international symposium on neuroblastoma screening. Stuttgart, 1995: 32.

25 Kushner BH, LaQuaglia MP, Ambros PF, et al. Survival from locally invasive or metastatic neuroblastoma (NB) without cytotoxic therapy (RX). *Proc Am Soc Clin Oncol* 1993; **12:** 413.

26 Brodeur GM, Hayes FA, Green AA, et al. Consistent N-*myc* copy number in simultaneous or consecutive neuroblastoma samples from 60 individual patients. *Cancer Res* 1987; **47:** 4248–53.

27 Carlsen NLT. Epidemiological investigations on neuroblastomas in Denmark 1943–1980. *Br J Cancer* 1986; **54:** 977–88.

28 Draper GJ, Kroll ME, Stiller CA. Childhood cancer. In: Cancer surveys. Vol 19/20: trends in cancer incidence and mortality. London: Imperial Cancer Research Fund, 1994: 493–517.

29 Esteve J, Parker L. Roy P, et al. Is neuroblastoma screening evaluation needed and feasible? *Br J Cancer* 1995; **71:** 1125–31.