

# Tonsillectomy and Hodgkin's Disease: Results From Companion Population-Based Studies<sup>1,2</sup>

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**ABSTRACT**—The question of whether persons with a history of tonsillectomy are at increased risk of Hodgkin's disease (HD) in adulthood was evaluated in companion population-based case-control studies conducted in the eastern Massachusetts and the Detroit metropolitan areas. These studies compared the history of tonsillectomy among incident cases with that of all their siblings by matched analysis controlling for confounding by childhood social class, family size, and birth order. Among young adults (15–39 yr) there is substantial evidence that tonsillectomy is not a risk factor and the relative risk (RR) is 1.0 (95% confidence interval, 0.72–1.4). Among middle-aged persons (40–54 yr) the RR is not significantly elevated, 1.5 (0.67–3.3), and the direction of the association differs between the sexes, consistent with the hypothesis of no association. Among older persons, the RR is significantly elevated, 3.0 (1.3–6.9), but the data are sparse. On the basis of these data, it appears unlikely that prior tonsillectomy is a causal factor in the development of HD in young and middle-aged adulthood. Whether it is a risk factor for the malignancy occurring late in life is unclear.—JNCI 1987; 78:1–5.

There have been conflicting reports concerning whether persons with a history of tonsillectomy have increased risk of HD (1–12). The question of this association is of special interest in light of the hypothesis that HD is an age-related consequence of a prevalent infection (13). In an attempt to resolve this controversy, we evaluated this association in two companion, population-based case-control studies conducted in eastern Massachusetts and in the Detroit metropolitan areas involving nearly 900 incident cases. The inclusion of two population bases permitted independent but comparable evaluations of the association. To control for the fact that tonsillectomy rates generally increase with level of social class as well as vary with local medical practices (14), we used siblings as controls.

## METHODS

**Boston-Worcester study population.**—We attempted to identify all persons first diagnosed with HD between July 1, 1973, and December 31, 1977, among the 3,098,000 residents of the Boston and Worcester Standard Metropolitan Statistical Areas in eastern Massachusetts ("Boston area") as previously described (15). Of the 447 cases diagnosed at age 15 or older, 326 (73%) were interviewed with the permission of their physicians. The distribution of all cases by interview status is summarized in table 1.

The procedures for interviewing the subjects are reported in detail elsewhere (16). Most interviews of cases (98%) were conducted in person, usually in the subject's home; 7 cases were interviewed by telephone or

questionnaire. As part of the interview, each case was asked for their own and their siblings' histories of tonsillectomy. At the end of the interview, each case was given a list of all questions and asked to discuss any uncertain information with other family members. Later, the interviewer telephoned the case and reviewed all information. In addition, the interviewer asked for permission to contact the two siblings closest in age to the case or the only sibling if appropriate. (Siblings <15 yr old and siblings whose age difference with the case was >12 yr were not included.)

We then attempted to obtain information from these sibling controls either by a personal interview (if they resided within a reasonable distance of Boston) or by a mail questionnaire. The information obtained included their tonsillectomy history and was verified by telephone follow-up. Of 481 potential sibling controls, 383 (80%) were interviewed. Of those interviewed, 81% were interviewed in person, 18% by questionnaire, and 1% by telephone alone. The disposition of all sibling controls is shown in table 2. Each interview was judged for its reliability. Of case interviews, 2% were judged to be less than "fairly reliable" as were less than 1% of sibling interviews.

**Detroit study population.**—Through the population-based cancer registry of the Division of Epidemiology, Michigan Cancer Foundation, we attempted to identify all persons first diagnosed with HD between July 1, 1973, through June 30, 1977, who were 15 years of age or older, among the 3,057,000 residents of the Detroit Standard Metropolitan Statistical Area. Of the 425 cases identified, information was obtained from 237 (56%)

ABBREVIATIONS USED: CI=confidence interval; HD=Hodgkin's disease; RR=relative risk.

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TABLE 1.—Percent distribution of cases according to interview status, age at diagnosis, and population

Status	Boston-Worcester			Detroit		
	15-39 yr	40-54 yr	≥55 yr	15-39 yr	40-54 yr	≥55 yr
Dead	3.4	11.6	41.7	15.2	35.6	62.6
Not located or moved out of area	1.9	0	0.9	5.9	2.7	0
Noninterviewable or unreliable	1.1	2.9	3.5	0	0	2.6
Physician refusal	1.1	2.9	7.0	3.8	2.7	6.1
Subject refusal	6.8	5.8	6.1	3.4	8.2	2.6
Interviewed	85.6	76.8	40.9	71.7	50.7	26.1
Proxy (No.)	—	—	—	(11)	(2)	(2)
Total percent	100.0	100.0	100.0	100.0	100.0	100.0
Total No.	263	69	115	237	73	115

with the permission of their physician. This information was obtained by a mail questionnaire that corresponded to the interview form used for the Boston area study population. Each respondent was telephoned to verify the information given. Fifteen questionnaires were completed by persons other than the case, mainly by mothers of young adults, including 6 respondents for cases who had died. The disposition of all cases is shown in table 1.

Sibling controls were identified by the same procedure as in the Boston area population. Information was obtained by questionnaire from 305 (89%) of 344 potential sibling controls including 20 by proxy, primarily from mothers of young adults (table 2). Of 176 case and 246 sibling interviews that were judged for reliability, none was rated less than "fairly reliable."

Ninety-three percent of all Boston area siblings interviewed reported the same tonsillectomy history for themselves as had been reported for them by their index case. The same percent agreement was found in the Detroit population. When there was a discrepancy, the sibling's report was used.

**Statistical analysis.**—Cases and their siblings are matched for sibship size and childhood social class, both potential confounding factors since they are associated with risk of HD (15) as well as with tonsillectomy rates (14). This matching by family proved necessary to maintain the analysis, inasmuch as the risk estimates based on matched and unmatched analyses differed. The method used was that of conditional logistic regression for matched data with the use of an algorithm and computer program developed by Dr. Bernard Rosner, Har-

vard Medical School. This method allows for a variable matching ratio and controls for confounding by additional unmatched factors. The algorithm has been published independently by Breslow et al. (17). In this matched data analysis, estimates of the measure of association between tonsillectomy and HD by the RR are based on the informative sets. This refers to those matched sets in which at least one sibling differs from the case in terms of tonsillectomy history. All RRs reported are maximum likelihood estimates. RR is the ratio of the incidence rate of HD among persons with a history of tonsillectomy to that among persons who did not have the operation. The 95% CIs of the RR were calculated by means of the variance estimated at the point estimate. When the interval does not include 1.0, the *P*-value associated with the estimate of RR is less than 0.05. Since social class risk factors for HD differ between age groups (15), the data were analyzed in 3 age groups based on the age at diagnosis of the index case: "young adults" (15-39 yr of age), "middle-aged" (40-54 yr), and "older" (≥55 yr). The analyses were first done with the use of all siblings as controls and then repeated with only those sibling controls who were interviewed. Results reported by sex refer to the sex of the cases in comparison to their siblings of both sexes.

## RESULTS

The overall tonsillectomy prevalence rate for cases and all their siblings combined is somewhat higher in the Boston area population (43%) than in the Detroit population (33%). For both populations, the tonsillect-

TABLE 2.—Percent distribution of sibling-controls according to interview status, age at diagnosis of index case, and population

Status	Boston-Worcester			Detroit		
	15-39 yr	40-54 yr	≥55 yr	15-39 yr	40-54 yr	≥55 yr
No permission to contact	7.4	25.4	37.8	1.6	6.0	16.7
Not located	0	3.0	0	1.6	4.0	2.8
Noninterviewable	0.3	1.5	0	0.8	0	2.8
Refusal	3.5	4.5	12.2	4.3	4.0	8.3
Interviewed	88.8	65.7	50.0	91.9	86.0	69.4
Proxy (No.)	—	—	—	(19)	(1)	—
Total percent	100.0	100.0	100.0	100.0	100.0	100.0
Total No.	340	67	74	258	50	36