Int. J. Cancer: **72,** 711–713 (1997)

Publication of the International Union Against Cancer
Publication de l'Union Internationale Contre le Cancer

RISK OF HODGKIN'S DISEASE SUBSEQUENT TO TONSILLECTOMY: A POPULATION-BASED COHORT STUDY IN SWEDEN

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Although some studies have linked excess of Hodgkin's disease (HD) to tonsillectomy, the findings have not been consistent. In particular, risk of HD by age at tonsillectomy has not been fully evaluated, despite the notable change in immunologic function of the tonsils between childhood and adulthood. To evaluate the risk of HD and other lymphomas, associated with tonsillectomy according to age at surgery, a population-based cohort study was conducted. Using nationwide Swedish hospitalization records, 55,169 patients undergoing tonsillectomy with/without adenoidectomy (T/A) were identified during the period 1964–1983. By linkage with the nationwide Total Population, Migration, Cancer and Causes-of-Death registries, these patients were followed up for as long as 25 years. After exclusion of the first post-operative year, a total of 533 first primary-cancer cases was identified between 1965 and 1989. Small excess risk was observed for HD (20 cases, SIR = 1.4, 95% CI 0.9–2.2). HD risk was more pronounced among patients tonsillectomized before age 12 (7 observed *vs.* 1.7 expected, SIR = 4.1, 95% CI 1.6–8.4), but declined significantly with older ages at T/A. While our data suggest a small increase in HD among all patients undergoing T/A and a significant excess for those under age 12 at surgery, we cannot exclude the possibility that the excess may be due to factors underlying the disorders that led to surgery. *Int. J. Cancer* 72:711–713, 1997.
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Although some studies have linked tonsillectomy with increased risk for Hodgkin's disease (HD) (Vianna *et al.,* 1971; Abramson *et al.,* 1978; Kirchhoff *et al.,* 1980), such findings were not reported in other studies (Johnson and Johnson, 1972; Newell *et al.,* 1973; Gledovic and Radovanovic, 1991). Despite the apparent decline in immunologic function of the tonsils from childhood to adulthood (Brandtzaeg, 1987; Andersson *et al.,* 1994), few studies have investigated the subsequent risk of HD associated with tonsillectomy according to the patient's age at surgery.

The Swedish nationwide hospitalization registration (Inpatient Register) offered a unique opportunity for evaluating the risk of HD and other cancers by age at tonsillectomy in a large population.

SUBJECTS AND METHODS

The methods utilized have been described in detail elsewhere (Nyren *et al.,* 1995). In brief, standardized information on hospitalizations was retrieved from the Swedish Inpatient Register for all 62,982 patients undergoing T/A (operation codes 2710 for tonsillectomy only and 2720 for tonsillectomy with adenoidectomy) from 1964 to 1983. After matching the hospitalization data with the nationwide Total Population, Migration and Causes-of-Death Registers, using each resident's unique 9-digit national registration number, 7,344 records were excluded because of incomplete or non-matching national registration numbers, inconsistent dates (of birth, hospitalization, cancer diagnosis, death and/or emigration) or death during the hospitalization for T/A.

The remaining 55,638 tonsillectomized patients were matched with the Swedish National Cancer Registry, listing virtually all incident cancer cases through 1989 (Mattsson *et al.,* 1985), and 855 patients were determined to have had a first primary cancer. From these we excluded 283 prevalent cancer cases diagnosed prior to the T/A. Also, 39 patients with incident cancers diagnosed within the first year after T/A were excluded, to minimize the possibility that the T/A performed was related to the presence of an undetected pre-clinical cancer. After exclusion of 147 patients who died or emigrated within the first year subsequent to the T/A, person-years at risk were calculated beginning 12 months after T/A, and terminating on the date of the first cancer diagnosis, emigration, death, or the end of the follow-up period (December 31, 1989), whichever came first.

Standardized incidence ratios (SIR), comparing the observed numbers of cancer cases with those expected, were used for estimating cancer risk following T/A. The expected numbers were derived by multiplying the person-years in each gender- , 5-year-age- and calendar-year-period stratum in the cohort by the corresponding nationwide site-specific cancer-incidence rates for Sweden from 1965 to 1989. Under the assumption that the observed number of cases follows a Poisson distribution, corresponding 95% confidence intervals (CI) were computed for each SIR (Bailar and Ederer, 1964). Stratified analyses were carried out to assess risk by age at T/A and at follow-up (age at HD diagnosis for the observed and age at risk for person-year calculation), interval between T/A and cancer diagnosis, and calendar-year period of the operation. A Chi statistic was used to test the significance of trends in SIRs with age at T/A (Breslow *et al.,* 1983).

RESULTS

Among the 55,169 tonsillectomized patients included in the final analysis (Table I), there were somewhat more women (56.6%) than men (43.4%), but there were no evident gender differences in mean age at T/A, calendar year of T/A, or number of years of follow-up (data not shown). Because of the lack of difference in patient characteristics and cancer risks by gender, males and females were combined for data analysis. Over 88% of all patients underwent T/A due to hyperplasia of the tonsils and/or adenoids. The entire cohort consisted of 10,733 (19.5%) patients tonsillectomized in childhood (<12 years), 23,084 (41.8%) in adolescence (12–19 years) and 21,352 (38.7%) in adulthood (≥20 years). Total cancer risk was not elevated (data not shown). A marginally significant 40% excess risk was observed both for HD and for non-Hodgkin's lymphoma (NHL).

Patients who had undergone surgery during childhood had a more-than-4-fold risk of HD, based on 7 cases, and the risk decreased significantly with older age at T/A (trend test, $p = 0.003$) (Table II). Among the 7 HD cases undergoing T/A before age 12, 4 had surgery at age 4, the others at ages 7, 9 and 11. Stratified analysis showed that T/A performed under age 5 was associated with a 20-fold increased risk of HD (SIR = 20, 95% CI 5.4–51.2) (Table II), while surgery performed between ages 5 and 11 was associated with an almost 2-fold increased risk (SIR = 1.8, 95% CI 0.4–5.8). All 7 cases were diagnosed as having HD before age 25, with an average of 10.7 years of follow-up between T/A and HD

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Received 17 June 1996; revised 21 April 1997

TABLE I – CHARACTERISTICS OF THE T/A COHORT, 1964–1989, SWEDEN

Characteristic				Total
Number of subjects in the cohort				55,169
Mean age at entry				19.5
Mean calendar year at entry				1976
Mean number of years of follow-up				13.4
Number of person-years by age at risk				
0–19				151,929
20–39				457,001
40–59				71,021
≥60				6,836
Total				686,787
Number of person-years by age and calendar year of tonsillectomy				
Age	<1970	1971–1974	1975–1979	≥1980
<12	1,951	10,035	20,308	88,985
12–19	5,475	28,237	60,850	206,355
≥20	4,060	22,806	52,693	185,032

diagnosis. Stratified analysis by age at follow-up revealed a statistically significant 3-fold excess risk before age 20, the risk declining with increasing age (Table II). The risk for HD increased as the cohort was followed for a longer time, with the highest among those followed for at least 10 years subsequent to the T/A.

A marginally significant 70% elevated risk for NHL was seen among patients undergoing T/A in adulthood, but only 4 NHL cases (out of 23) occurred in patients who had had surgery before age 20 (data not shown). Consistent with the findings of HD, the risk of NHL rose with increasing length of follow-up, and was highest among those followed for a 10 or more years (SIR = 1.6, 95% CI 0.9–2.7). Analysis by calendar-year of T/A (before 1970, 1970–1974, 1975–1979 and after 1979) revealed no clear secular pattern of risks for either HD or NHL (data not shown).

DISCUSSION

In this largest T/A cohort with long-term follow-up to date, we found no overall elevated risk for all cancers and only a marginally significant 40% excess of HD among 55,169 tonsillectomized patients in Sweden. The excess risk for HD, although based on small numbers, was more pronounced among those undergoing T/A during childhood, particularly before age 5. A small marginally significant excess of NHL was observed, mostly due to elevated risk among those undergoing T/A in adulthood.

Many viral infections, including Epstein-Barr virus (EBV), have been postulated as being etiologically linked with HD (Jarrett, 1992; Niedobitek and Young, 1994). However, most of these infections are common, while HD is a rare outcome, suggesting that other factors may be involved in HD development. It has been suggested that the role of tonsillar tissue in immune function is most important in childhood and declines markedly after age 20 (Brandtzaeg, 1987; Andersson *et al.*, 1994). Therefore, it is possible that increased risk of HD is associated with a potential alteration in immune status subsequent to T/A at young ages in conjunction with certain viral infections. Alternatively, the increased risk for HD may be due to some underlying factors that predispose to HD and to recurrent pharyngeal infections necessitating T/A, rather than to the surgery itself. Among the many possible underlying causes of recurrent pharyngeal infections is EBV, which has been linked to recurrent tonsillitis (Sprinkle and Veltri, 1976; Yamanaka and Kataura, 1984). In addition, medical treatments that may increase the use of T/A and the risk of HD should be considered. The possibility of a chance finding cannot be totally excluded, since the observed number of HD is rather small. In contrast to our findings, the only prior study of HD risk according to age at T/A reported a protective effect for HD associated with T/A at an early age (Bonelli *et al.*, 1990).

Compared with the median age at HD diagnosis in Sweden (54–59 years old), the median age (24.5 years) was much younger in our cohort. Assuming that the association we observed is real, the higher risk linked with longer follow-up suggests that more HD cases may be expected as the cohort ages. The higher risk seen among HD cases with diagnosis prior to age 20 may reflect young age at T/A (the median age at T/A being 6.5 years among those diagnosed with HD before age 20).

It has been suggested that socioeconomic status (SES) may confound the association between T/A and HD, since higher SES has been linked with increased risk of HD and higher rates of T/A in the U.S. (Gutensohn and Cole, 1981). However, an earlier Swedish study (Hardell and Bengtsson, 1983) did not find SES to be a risk factor for HD, suggesting the lack of confounding by SES on the T/A-HD association in the Swedish population. In addition, the widespread accessibility of excellent medical care at minimal cost to all Swedish residents throughout the study period is likely to have minimized the potential influence of SES on physicians' recommendations and on patients' (or parents') decisions regarding T/A. Moreover, since risks of HD were increased only 2-fold among patients in the higher SES group (Gutensohn and Cole, 1981), potential confounding by SES could not explain the 4-fold excess among those undergoing T/A before age 12 in our study (Yanagawa, 1984; Wacholder, 1995).

Among the limitations that must be considered are lack of information on potential confounders (such as SES and viral infections) (Jarrett, 1992; Niedobitek and Young, 1994; Hardell

TABLE II – STANDARDIZED INCIDENCE RATIOS (SIR) AND CORRESPONDING 95% CONFIDENCE INTERVALS (CI) FOR HD BY AGE AT T/A, AGE AT HD DIAGNOSIS, AND LENGTH OF FOLLOW-UP, 1964–1989, SWEDEN

					Median among HD cases		
	Observed	Expected	SIR	95% CI	Age at T/A	Age at HD	Years of follow-up
Total	20	14.3	1.4	0.9–2.2	15	24.5	9.6
Age at T/A							
<12	7	1.7	4.1	1.6–8.4	4	18	10.0
<5	4	0.2	20.0	5.4–51.2	4	16	11.8
5–11	3	1.7	1.8	0.4–5.8	9	18	8.2
12–19	9	6.9	1.3	0.6–2.5	16	26	9.2
≥20	4	5.7	0.7	0.2–1.8	21	34.5	7.5
Age at follow-up (HD diagnosis)							
<20	6	2.0	3.0	1.2–6.2	6.5	15	7.8
20–29	10	7.0	1.4	0.7–2.5	16	25	9.7
≥30	4	4.4	0.9	0.3–2.2	21	35.5	13.8
Time between T/A and HD diagnosis							
<4 years	3	3.1	1.0	0.2–2.9	20	24	1.7
4–9 years	6	5.4	1.1	0.4–2.4	12.5	19.5	7.6
≥10 years	11	5.9	1.9	0.9–3.3	16	26	12.6

and Bengtsson, 1983) and the absence of information on histologic sub-types of HD, while misclassification between HD and NHL has also been recognized (Martinsson *et al.*, 1992). The average age of the cohort members at T/A was 19.5 years, and the mean follow-up time was 13.4 years; thus, most of the cohort members were followed only into their 30s and 40s. Although we were able to evaluate the first peak of HD occurring between ages 15 and 39, we could not fully assess the second peak of HD generally occurring after age 70. While the study population was confined to hospitalized patients, analysis by calendar year of T/A did not demonstrate differences in risk between the earlier and later periods, when substantially higher proportions of T/A were performed as an outpatient procedure.

In summary, we observed a modest increase in risk for HD, particularly associated with younger age at T/A, which needs to be confirmed in other large studies utilizing medical records. Although the previous US studies have attributed the risk for tonsillectomy-associated HD to the confounding effects of SES, our results suggest an alternative explanation. If validated excesses of HD are seen following T/A in other populations, it may be that some hitherto unidentified immune function of tonsils among young children could be involved. Assuming that our findings are confirmed, evaluation of the association between T/A and HD would require detailed investigation of other potential confounding factors (such as SES and etiologic viral infections), possible effect modifiers, tonsil-related immune function and genetic susceptibility, as well as genetic-environmental interactions. While evaluation of underlying mechanisms would be helpful in clarifying reasons for the association of T/A with HD, it is important to recognize that the very small attributable risk should not discourage medically necessary T/A. However, such risk may be further reduced if T/A can be postponed from an early to a later period in childhood.

ACKNOWLEDGEMENTS

We are thankful to Dr. J.F. Fraumeni Jr. and Dr. S. Wacholder for their comments and to Mr. J. Hoefling and Ms. S. Keehn at IMS, Inc., for data processing.

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