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Cancer after repair of esophageal atresia: population-based long-term follow-up

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Abstract

Objective: Esophageal atresia (EA) predisposes to gastroesophageal reflux that is associated with intestinal metaplasia and may result in development of adenocarcinoma of the esophagus. To date, the literature has reported 5 cases of esophageal cancer in adult patients treated for EA. The aim of this study was to find out the incidence of esophageal cancer in adult patients with repaired EA.

Patients and Methods: Five hundred two consecutive patients treated for EA from 1949 to 1978 were followed-up for cancer through the files of the population-based countrywide cancer registry from 1967 to 2004. The number of cancer cases observed and person-years at risk were counted, and the expected number of cancer cases estimated from the national cancer incidence rates. The standardized incidence ratios (SIRs) were calculated by dividing the number of cancer cases observed by the expected numbers.

Results: None of the 502 patients were lost to follow-up; 230 patients who died before 1967 younger than the median age of 8 days were excluded from further analysis. The 272 remaining patients (142 males) were eligible for follow-up (median age, 35 years; range, 2 days to 56 years). Three cases of cancer were found (SIR, 1.0; 95% confidence interval, 0.20-2.8). One was lymphoma in small intestine, 1 was leukemia, and 1 carcinoma of the uterus but no cases of esophageal cancer.

Conclusions: Our study is able to exclude long-term risk for esophageal cancer after repair of EA 500-fold higher than that of the normal population. Considering the relatively young age of the survivors, further studies and continued follow-up are warranted to elucidate risk for esophageal cancer and need for endoscopic surveillance after repair of EA.

Esophageal atresia (EA) and its surgical repair disturb the anatomy and innervation of the esophagus. Altered esophageal motility and function may predispose to gastroesophageal reflux (GER). In fact, GER is a frequent finding after surgical repair of EA [1-16]. It is believed that continuing reflux of acidic stomach secretions into the esophagus causes inflammation, metaplasia, dysplasia, and eventually adenocarcinoma [17-25]. Endoscopic follow-up studies of adult EA patients have demonstrated esophagitis [4,6], intestinal metaplasia [1,9,10,12], and even cases of esophageal carcinoma [12]. The total of esophageal cancer cases reported to date among adult EA patients has been only 5 [26-30]. To this end, we performed a population-based

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prospective long-term follow-up for esophageal cancer and other cancers in patients with EA.

1. Methods

All consecutive patients operated on for EA during infancy at the Hospital for Children and Adolescents, University of Helsinki, Helsinki, Finland, between the years 1949 and 1978 were included in the study cohort. Patients were identified by review of operating theater diaries for the diagnosis and the surgical procedure of every patient operated on in our hospital since 1946. For descriptive purposes, we retrospectively collected information concerning survival, type of EA, and surgical treatment. We considered a patient as surviving if he or she had initially been discharged alive. The data came from the hospital records by means of a standardized data extraction sheet. Ethics committee of Hospital for Children and Adolescents, University of Helsinki, Finland, has approved this study, and the study complies with the Declaration of Helsinki.

The follow-up for cancer started at the date of each subject's birth or on January 1, 1967, whichever was later, and ended upon the subject's death or on December 31, 2004, whichever occurred first. Since January 1, 1967, all residents of Finland have had a unique personal identification (ID) code. The individuals in the study cohort were compared with those listed under the Population Register Center of Finland, and the correctness of each ID code and vital status was checked. If a patient was not identified by name and date of birth from the Population Register Center of Finland, an additional search was conducted based on parents' names and place of birth.

Follow-up for cancer was performed automatically based on the IDs, in a linkage with the population-based country-wide Finnish Cancer Registry. The Finnish Cancer Registry maintains records of all cancer patients from every medical facility in Finland and has practically complete coverage and high accuracy [31].

The number of cases observed and the number of person-years at risk were counted in 5-year age groups separately for both sexes and 4 calendar periods (1967-1976, 1977-1985, 1986-1995, 1996-2004). The expected number of cancer cases was calculated by multiplying the number of person-years in each stratum by the corresponding cancer incidence in all of Finland. To calculate the standardized incidence ratio, the number of cases observed was divided by the expected number. Exact 95% confidence intervals (CIs) were defined on the assumption that the number of cases observed followed a Poisson distribution.

Table 1 Number of patients operated on for EA in Finland and percentages of patients discharged from hospital alive by year of operation

Y	No. of patients	Survival (%)
1947-1956	100	19
1956-1960	100	43
1960-1965	101	56
1965-1971	101	70
1971-1978	100	85

Table 2 Person-years at risk among Finnish patients with EA in 1967 to 2004 by age and sex

Age (y)	Males (n = 142)	Females (n = 130)	All (N = 272)
0-14	1590	1312	2902
15-29	1831	1527	3358
30-44	905	732	1637
45-59	80	57	137
Total	4406	3628	8034

2. Results

We identified 502 patients. Overall survival was 54% with steady improvement over the decades (Table 1). Of the patients, 88% had EA with a distal fistula, 7.8% had EA without a fistula, and 2.0% had tracheoesophageal fistula without EA. The rest comprised of rare variants of the anomaly. Of the 502, 29 patients had their esophagus substituted with colon or gastric tube. The rest had a native esophagus in situ.

No patient was lost to follow-up; 230 patients who had died before 1967 (before follow-up began) younger than the median age of 8 days (range, 1 day to 8.3 years) were excluded from further analysis. The 272 remaining patients (142 males) were eligible for follow-up. The median age of the eligible patients at the end of the follow-up was 35 years (range, 2 days to 56 years). The number of person-years at risk was 8034 (Table 2). Three cases of cancer were observed vs 3.1 expected (Table 3). These included 1 small intestinal lymphoma, 1 leukemia, and 1 carcinoma of the uterus. We found no cases of esophageal cancer (95% CI, 0-500), gastric cancer (95% CI, 0-63), lung cancer (95% CI, 0-62), or laryngeal cancer (95% CI, 0-580).

Table 3 Observed and expected numbers of all cancer cases and standardized incidence ratios (SIRs) with their 95% CI among Finnish patients with EA in 1967 to 2004

Age (y)	Observed	Expected	SIR	95% CI
0-14	-	0.4	0.0	0.0-9.4
15-29	1	0.9	1.1	0.0-6.1
30-44	2	1.4	1.4	0.2-5.0
45-59	-	0.4	0.0	0.0-8.8
Total	3	3.1	1.0	0.2-2.8