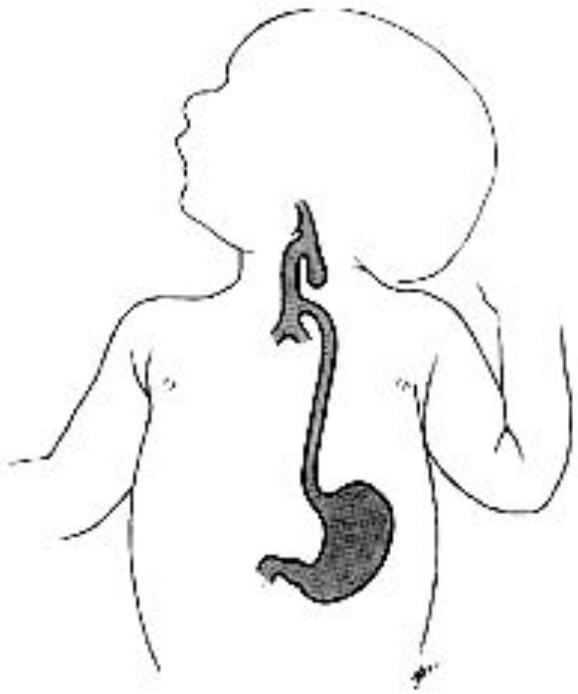
Long-Term Outcomes of Esophageal Atresia

« Ruokatorven synnynnäisen puutoksen myöhäisvaikutukset »

Saara Sistonen

Academic Dissertation



Supervisors

Docent Mikko P. Pakarinen
Section of Pediatric Surgery
Hospital for Children and Adolescents
University of Helsinki
Finland

Professor Risto J. Rintala
Section of Pediatric Surgery
Hospital for Children and Adolescents
University of Helsinki
Finland

Reviewers

Docent Markku Luostarinen
Department of Surgery
Päijät-Häme Central Hospital
Lahti
Finland

Docent Tomas Wester
Department of Pediatric Surgery
Karolinska University Hospital
Stockholm
Sweden

Opponent

Professor Agostino Pierro
UCL Institute for Child Health and Great Ormond Street Hospital for Children
London
United Kingdom

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Long-Term Outcomes of Esophageal Atresia

Saara Sistonen

Department of Pediatric Surgery
University of Helsinki
Finland

and

Pediatric Graduate School
Hospital for Children and Adolescents
University of Helsinki

and

National Graduate School of Clinical Investigations

ACADEMIC DISSERTATION

To be publicly discussed with the permission of the Medical Faculty, University of Helsinki,
in the Niilo Hallman auditorium of the Hospital for Children and Adolescents
On 23th April 2010, at 12 noon.

Helsinki 2010

HUCH Paediatric Surgery
HOSPITAL DISTRICT OF HELSINKI AND UUSIMAA

CLIGS National Graduate School of Clinical Investigation

VKTK Valtakunnallinen kliininen tutkijakoulu

"In the fifties newborns were fed with sugarwater. Sugar water in the lungs resulted in breathing problems. A three-day-old baby was sent by car to Helsinki from a little town in central Finland. The referring doctor suggested that the ride would not reach its destination early enough, and the baby would probably die before that. They ran out of oxygen in the wooden incubator when reaching Porvoo. At the Children´s Hospital in Helsinki staff was already awaiting out front, and intravenous liquid treatment was started right away. The operation was performed the day after, and it lasted four hours. The mother was allowed to hold the baby in her arms the day before discharge, when the baby was over three months old."

From a letter from an adult patient with repaired esophageal atresia

"1950-luvulla vastasyntyneille annettiin sokerivettä. Hengitysvaikeuksia oli tullut, kun sokerivettä oli joutunut keuhkoihin. Vastasyntynyt oli lähetetty 3 vuorokauden iässä autokyydillä Helsinkiin pienestä keskisuomalaisesta kylästä. Lähettänyt lääkäri oli arvioinut, ettei kyyti ehtisi ajoissa perille vaan vauva ehtisi kuolla ennen sitä. Vanerista tehdyn keskoskaapin happipullosta oli loppunut happi Porvoon kohdalla. Lastenklinikan ovella oltiin jo vastassa perille saavuttaessa ja suoniyhteys oli avattu heti ja annettu ravintoliuosta. Leikkaus tehtiin seuraavana päivänä ja se kesti 4 tuntia. Äiti sai ottaa vauvan syliin ensimmäisen kerran vasta päivää ennen kotiutumista, yli 3 kuukauden kuluttua vauvan syntymästä."

Ote kirjeestä aikuiselta ruokatorviatresiapotilaalta

Table of Contents

Abstract

BACKGROUND AND OBJECTIVE

Esophageal atresia (EA), a common congenital anomaly comprising interrupted esophagus with or without a tracheoesophageal fistula (TEF), affects one in 2840 newborns. Over half have associated anomalies. Malformations affecting the midline – vertebral column, cleft lip and palate, septal defects of the heart, tracheoesophageal and anorectal malformations, as well as ear, renal, and limb anomalies, are typically associated with EA. After EA repair in infancy, gastroesophageal reflux (GER) and esophageal dysmotility and respiratory problems are common. As there exist no previous population-based long-term follow-up-studies on EA, its long-term sequelae are unclear. To date, worldwide, six cases of esophageal cancer have been reported in young adults treated for EA. Clinical characteristics of spinal deformities that commonly occur in adults with repaired EA are unknown. The aims of this study were to assess the *cancer incidence (I), esophageal morbidity and function (II)*, *respiratory morbidity (III),* and the natural history of *spinal defects (IV)* in adults with repaired EA.

PATIENTS AND METHODS

All 588 patients treated for EA at the Hospital for Children and Adolescents, University of Helsinki, from 1947 to 1985 were identified through patient record review and the files of the Population Register Centre of Finland. Those 235 patients alive with their native esophagus were contacted, and the first hundred who replied and agreed to participate in the study made up the study group. The patients were interviewed, they filled in symptom questionnaires including esophageal, respiratory, and musculoskeletal symptoms, and they underwent esophageal endoscopy with biopsies and esophageal manometry, pulmonary function tests (PFT) including flow volume spirometry, a histamine challenge test (HCT), an exhaled nitric oxide test (FE^{NO}), and a skin prick test (SPT) for common allergens. In addition, full orthopedic evaluation was performed with radiographs of the spine. The questionnaire was also sent by mail to adults with repaired EA not attending the clinical study, and to 287 general population-derived controls matched for age, gender, and municipality of residence. Incidence of cancer among the study population was evaluated from the population-based countrywide cancer registry.

RESULTS

Patients: Of the 235 patients contacted, 169 (72%) replied; 101 (42%) adults with repaired EA (58 male) participated in the clinical studies at a median age of 36 years (range, 22-56).
Cancer: Despite the high incidence of esophageal metaplasia, none of the Finnish EA patients had suffered esophageal cancer, according to the Finnish Cancer Registry. Although three had had cancer (SIR, 1.0; 95% CI, 0.20-2.8), one was lymphoma in the small intestine, one leukemia, and one carcinoma of the uterus; but no cases of esophageal cancer occurred. The overall cancer incidence among adults with repaired EA did not differ from that of the general Finnish population.
Esophageal Morbidity: Symptomatic GER occurred in 34% and dysphagia in 85% of the patients and in 8% and 2% of the controls ($P<0.001$ for both). The main endoscopic findings included hiatal hernia (28%), Barrett´s esophagus (11%), esophagitis (8%), and stenotic anastomosis (8%). Histology revealed esophagitis in 25 individuals, and epithelial metaplasia in another 21. Epithelial metaplasia was associated with esophagitis in 7 of the 21 cases. At immunohistochemistry, CDX2-positive columnar epithelial metaplasia was present in all 21 individuals, and 6 of these also

demonstrated goblet cells and MUC2 positivity. In all histological groups, GER and dysphagia were equally common (P=ns). Esophageal manometry demonstrated non-propagating peristalsis in most of the patients, and low ineffective pressure of the distal esophageal body in all. The changes were significantly worse in those with epithelial metaplasia (P≤0.022). Anastomotic complications (OR 8.6-24, 95%CI 1.7-260, P=0.011-0.008), age (OR 20, 95%CI 1.3-310, P=0.034), low distal esophageal body pressure (OR 2.6, 95%CI 0.7-10, P=0.002), and defective esophageal peristalsis (OR 2.2, 95%CI 0.4-11, P=0.014) all predicted development of epithelial metaplasia.

Respiratory Morbidity: Current respiratory symptoms occurred in 11% of the patients and 2% of the controls (P<0.001). Of the patients, 16%, and 6% of the controls had doctor-diagnosed asthma (P<0.001). A total of 56% and 70% of the patients and 20% and 50% of the controls had a history of pneumonia and of bronchitis (P<0.001 for both). Respiratory-related impaired quality of life was observable in 11% of the patients in contrast to 6% of the controls (P<0.001). PFT revealed obstruction in 21 of the patients, restriction in 21, and both in 36. A total of 41 had bronchial hyper-responsiveness (BHR) in HCT, and 15 others had an asthma-like response. FE^{NO} revealed airway inflammation in another 11. Thoracotomy-induced rib fusion (OR 3.4, 95%CI 1.3-8.7, P=0.01) and gastroesophageal reflux-associated epithelial metaplasia in adulthood (OR 3.0, 95%CI 1.0-8.9, P=0.05) were the most significant risk factors for restrictive ventilatory defect.

Musculoskeletal Defects: Vertebral anomalies were evident in 45 patients, predominating in the cervical spine in 38. The most significant risk factor for the occurrence of vertebral anomalies was any additional anomaly (OR 27, 95%C I8-100). Scoliosis (over 10 degrees) was observable in 56 patients, over 20 degrees in 11, and over 45 degrees in one. In the EA patients, risk for scoliosis over 10 degrees was 13-fold (OR 13, 95%CI 8.3-21) and over 20 degrees, 38-fold (OR 38, 95%CI 14-106) when compared to that of the general population. Thoracotomy-induced rib fusion (OR 3.6, 95%CI 0.7-19) and other associated anomalies (OR 2.1, 95%CI 0.9-2.9) were the strongest predictive factors for scoliosis. However, the general clinical course of spinal deformities was mild, and none of the patients has undergone spinal surgery.

CONCLUSIONS

Significant esophageal morbidity associated with EA extends into adulthood. No association existed between the esophageal symptoms and histological findings. Surgical complications, increasing age, and impaired esophageal motility predicted development of epithelial metaplasia after repair of EA. Esophageal anastomotic complications appear to further impair esophageal motility and GER, both of which predispose to development of esophageal epithelial metaplasia, as does increasing age. According to our data, the risk for esophageal cancer is not higher than 500-fold that of the general population. However, the overall cancer incidence among adults with repaired EA did not differ from that of the general Finnish 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. Adults with repaired EA have had significantly more respiratory symptoms and infections, as well as more asthma and allergies than does the general population. Nearly half the patients have BHR. Thoracotomy-induced rib fusion and gastroesophageal reflux-associated columnar epithelial metaplasia were the most significant risk factors for the restrictive ventilatory defect that occurred in over half the patients. Over half the patients with repaired EA are likely to develop scoliosis. Risk for scoliosis is 13-fold after repair of EA in relation to that of the general population. Nearly half the patients have had vertebral anomalies predominating in the cervical spine, and of these, most were vertebral fusions. Most of these deformities were diagnosed neither in infancy nor during growth. The natural history of spinal deformities seems, however, rather benign, with spinal surgery rarely indicated.

Tiivistelmä

TAUSTA JA TARKOITUS

Esofagusatresia (EA) on melko yleinen ruokatorven synnynnäinen kehityshäiriö, jossa ruokatorven yläosa muodostaa umpipussin, jonka lisäksi ruokatorven ja henkitorven välillä on yleensä yhdyskanava. Ruokatorviatresian ilmaantuvuus on 1 : 2840 vastasyntynyttä. Yli puolella on lisäksi jokin muu kehityshäiriö. Keskiviiva-anomaliat, kuten selkärankamuutokset, kita- ja suulakihalkio, sydämen väliseinäkehityshäiriöt, ruokatorvi-henkitorvikehityshäiriöt, peräaukon ja peräsuolen kehityshäiriöt, sekä korva-, munuais- ja raajamuutokset, ovat tavallisia oheisepämuodostumia. Mahanesteen takaisinvirtaus ruokatorveen ja ruokatorven toimintahäiriöt sekä hengitystieongelmat ovat tavallisia ongelmia lapsuudessa ruokatorviatresian korjausleikkauksen jälkeen. Aiheesta ei ole aiemmin tehty väestöpohjaisia pitkäaikaisseurantatutkimuksia, joten pitkäaikaisvaikutuksista ei ole luotettavaa tietoa. Kirjallisuudessa on esitetty kuusi ruokatorvisyöpätapausta nuorilla aikuisilla, joille on vastasyntyneenä tehty ruokatorviatresian korjausleikkaus. Myöskään ruokatorviatresiaan liittyvät selkärankaviat ja niiden luonnollinen kulku eivät ole tunnettuja. Tutkimuksen tavoitteena oli selvittää *syövän esiintymistä (I), ruokatorviperäistä sairastavuutta ja ruokatorven toimintaa (II), hengitystieperäistä sairastavuutta (III)* ja ruokatorviatresiaan liittyviä *selkärangan poikkeavuuksia (IV)* aikuisiällä ruokatorviatresian korjauksen jälkeen.

POTILAAT JA MENETELMÄT

Kaikki 588 ruokatorviatresian vuoksi Helsingin Lastenklinikalla vuosina 1947-1985 hoidettua henkilöä tunnistettiin vertaamalla potilasasiakirjatietoja Väestörekisterikeskuksen tietoihin. Elossa oleviin 235 henkilöön, joille oli tehty ruokatorviatresiakorjaus omalla ruokatorvella otettiin yhteyttä, ja ensimmäiset sata kyselyyn vastannutta henkilöä, jotka olivat halukkaita osallistumaan tutkimuksiin otettiin mukaan tutkimukseen. Potilaat haastateltiin, he täyttivät oirekyselyn liittyen ruokatorvi-, hengitytie- sekä tuki- ja liikuntaelinoireisiin ja vaivoihin, ja heille tehtiin ruokatorven tähystys ja ruokatorven toimintakoe, keuhkojen toimintakokeita, histamiinialtistus (HA), uloshengityksen typpioksipitoisuusmittaus (FE^{NO}), ihopistokokeita, sekä lisäksi perusteellinen ortopedinen tutkimus selkärankaröntgenkuvineen. Kyselykaavakkeet lähetettiin postikyselynä myös niille tutkimusjoukkoon kuuluville henkilöille, jotka eivät osallistuneet kliinisiin tutkimuksiin, sekä 287:lle väestörekisteristä satunnaisesti poimitulle ikä-sukupuoli-syntymäkotikunta-vakioiduille henkilölle. Syövän esiintymistä tutkimusjoukon henkilöillä selvitettiin yhteistyössä Syöpärekisterin kanssa.

TULOKSET

Potilaat: 235 tutkimusjoukkoon kuuluuvasta henkilöstä kaikkiaan 169 (72%) vastasi kyselyyn. 101 (43%) henkilöä (58 miestä) osallistui kliinisiin tutkimuksiin 36 (vaihteluväli, 22 – 56) vuoden iässä.
Syöpä: Yhtään ruokatorvisyöpää ei todettu. Ruokatorviatresia-aikuispotilaista kolmella oli ollut syöpä: yhdellä ohutsuolen lymfooma, toisella leukemia ja kolmannella kohtusyöpä. Syövän esiintymisessä ei ollut eroa verrattuna syövän esiintymiseen suomalaisilla yleensä.
Ruokatorviperäinen sairastavuus: Merkittäviä gastroesofageaalisen refluksin oireita oli 34%:lla ja nielemisvaikeuksia 85%:lla potilaista sekä 8%:lla ja 2%:lla vertailuhenkilöistä. Päälöydökset ruokatorven tähystyksessä olivat palleatyrä (28%), Barretin ruokatorvi (11%), ruokatorvitulehdus (8%) sekä ruokatorven ahtauma (8%). Immunohistokemiallisissa tutkimuksissa ilmeni ruokatorvitulehdus 25%:lla ja ruokatorvilimakalvon korvautuminen CDX2-positiivisella mahalaukkutyyppisellä limakalvolla (ns. epiteliaalinen metaplasia) 21%:lla, sekä MUC2-positiivinen

intestinaalinen metaplasia pikarisoluineen 6%:lla. Epiteliaaliseen metaplasiaan liittyi ruokatorvitulehdus seitsemässä tapauksessa 21:stä. Ruokatorven limakalvomuutoksilla ei ollut yhteyttä ruokatorvioireiden esiintymiseen. Ruokatorven manometriassa ilmeni, että valtaosalla potilaista ruokatorven toiminta ei ollut peristalttista, ja kaikilla oli matalat ruokatoren runkopaineet muutosten ollessa merkittävimmät niillä, joilla todettiin ruokatorven metaplasia. Erot eri ryhmien välillä oli merkitseviä. Ruokatorviliitoksen komplikaatiot, ikä, matalat ruokatorven runkopaineet, sekä huono ruokatorven peristalttinen toiminta ennustivat ruokatorven epiteliaalisen metaplasian ilmaantumista.

Hengitystieperäinen sairastavuus: Viimeaikaisia hengitystieoireita esiintyi potilailla (11%) enemmän kuin verrokeilla (2%). 16%:lla tutkimushenkilöistä ja 6%:lla verrokeista oli diagnosoitu astma. Keuhkokuume ja keuhkoputkitulehdus oli ollut 56%:lla ja 70%:lla tutkimushenkilöistä sekä 20%:lla ja 50%:lla verrokeista. Hengitystieoireisiin liittyen elämänlaatu on heikentynyt 11%:lla tutkimushenkilöistä ja 6%:lla verrokeista. Erot eri ryhmien välillä oli merkitseviä. Keuhkojen toimintakokeessa 21%:lla tutkimushenkilöistä oli obstruktio ja 21%:lla oli restiriktio sekä molemmat oli 36%:lla. Lisäksi 41%:lla todettiin keuhkoputkien supisteluherkkyys HA:ssa ja 15%:lla tuli esille astmaan sopiva keuhkoputkien hyperreaktiviteettireaktio. FE^{NO}:ssa 11%:lla tutkimushenkilöistä todettiin keuhkoputkien inflammaatio. Ruokatorviatresian korjausleikkauksen jälkeinen kylkiluiden yhteensulautuminen sekä kirurgisten komplikaatioiden jälkeinen ruokatorven refluksista johtuva epiteliaalinen metaplasia ennustivat restriktion esiintymistä.

Tuki- ja liikuntaelinviat: Selkärangan nikamakehityshäiriöitä todettiin 45%:lla potilaista, valtaosalla kaularangan alueella, kaikkiaan 38%:lla. Minkä tahansa muun lisäanomalian esiintyminen ruokatorviatresiaan liittyen ennusti merkitsevästi nikama-anomalioiden esiintymistä. Yli 10° skolioosi todettiin radiologisesti 56%:lla, yli 20° skolioosi 11%:lla, ja yli 45° skolioosi 1%:lla. Yli 10° skolioosin riski oli 13-kertainen, ja yli 20° skolioosin riski 38-kertainen keskivertoväestöön verrattuna. Ruokatorviatresian korjausleikkaukseen liittyvät kylkiluiden yhteensulautumat ja muut lisäanomaliat olivat vahvimpia ennustetekijöitä skolioosin esiintymiselle. Yleensä ottaen selkärankaviat olivat kuitenkin lieviä, eikä kenellekään oltu tehty selkärankakorjausleikkausta.

JOHTOPÄÄTÖKSET

Ruokatorviperäiset vaivat jatkuvat aikuisiällä ruokatorviatresiakorjauksen jälkeen. Ruokatorvioireilla ja ruokatorven limakalvomuutoksilla ei ollut yhteyttä. Ruokatorviliitoksen komplikaatiot huonontavat edelleen ruokatorven toimintaa ja refluksia, jotka yhdessä ikääntymisen ohella ennustivat ruokatorvilimakalvomuutoksia aikuisiällä ruokatorviatresian korjauksen jälkeen. Syövän esiintymisessä ruokatorviatresian jälkeen ei ollut eroa keskivertoväestöön verrattuna. Tutkimuksemme perusteella tilastollinen ruokatorvisyöpäriski on alle 500-kertainen ruokatorviatresian korjauksen jälkeen verrattuna suomalaisiin yleensä. Ottaen huomioon ruokatorviatresian vuoksi leikattujen henkilöiden suhteellisen nuoren iän jatkotutkimukset ovat tarpeen ruokatorvisyöpäriskin selvittämiseksi ja tähystysseurannat ovat suositeltavia. Ruokatorviatresia-aikuispotilailla on merkittävästi enemmän hengitystieoireita ja hengitystieinfektioita sekä astmaa ja allergioita keskivertoväestöön verrattuna. Yli puolella ruokatorviatresia-aikuispotilaista esiintyvää keuhkojen restriktiota selittävät ruokatorviatresian korjausleikkauksen jälkeiset kylkiluiden yhteensulautumat sekä refluksista aiheutuvat limakalvomuutokset. Puolelle ruokatorviatresia-aikuispotilaista kehittyy selän ryhtivirhe eli skolioosi, ja sen riski on 13-kertainen keskivertoväestöön verrattuna. Lähes puolella on nikamakehityshäiriö. Valtaosaa näistä muutoksista ei oltu diagnosoitu lapsuudessa tai kasvun aikana. Kuitenkin selkärankavikojen luonnollinen kulku vaikuttaa melko hyvänlaatuiselta, ja selkärankakirurgia on harvoin aiheellista.

Abbreviations

ASD	atrial septal defect
BHR	bronchial hyperresponsiveness
CDX2	intestinal transcriptor factor, mucine-coding protein
CI	confidence interval
DDA	doctor-diagnosed asthma
EA	esophageal atresia
FE^{NO}	exhaled nitric oxide level
FEV1	forced expiratory volume in one second
FVC	forced vital capacity
GIQLI	gastrointestinal quality of life index
GER	gastroesophageal reflux
GSRS	gastroesophageal symptom rating scale
HCT	histamine challenge test
Ig	immunoglobulin
IHC	immunohistochemistry
IQR	interquartile range
kU/L	kilounit per litre
MUC2	mucus secreting goblet cell-mucine marker MUC2
OR	odds ratio
PDA	patent ductus arteriosus
PD15FEV1	provocative dose of histamine causing a 15% fall in FEV1
PF, PFT	pulmonary function, pulmonary function test
RSRQLI	respiratory symptom-related quality of life index
Shh	Sonic hedgehog
SIR	standardized incidence ratio
SPT	skin prick test
TEF	tracheoesophageal fistula
VACTERL	multianomaly association with vertebral, anorectal, cardiac, tracheoesophageal, renal and limb defects
VSD	ventricular septal defect

Original publications

This thesis is based on the following publications:

I Sistonen SJ, Koivusalo A, Lindahl H, Pukkala E, Rintala RJ, Pakarinen MP: Cancer after repair of esophageal atresia: Population-based long-term follow-up. *Journal of Pediatric Surgery 2008;43:602-605.*

II Sistonen SJ, Koivusalo A, Nieminen U, Lindahl H, Lohi J, Kero M, Kärkkäinen P, Färkkilä MA, Sarna S, Rintala RJ, Pakarinen MP: Esophageal morbidity and function in adults with repaired esophageal atresia: A population-based long-term follow-up. *Annals of Surgery 2010.* In press.

III Sistonen SJ, Malmberg LP, Malmström K, Haahtela T, Rintala RJ, Pakarinen MP: Repaired esophageal atresia: respiratory morbidity and pulmonary function in adults in a population-based long-term follow-up. *European Respiratory Journal 2010.* In press.

IV Sistonen SJ, Helenius I, Peltonen J, Sarna S, Rintala RJ, Pakarinen MP: Natural history of spinal anomalies and scoliosis associated with esophageal atresia. *Pediatrics 2009;124:e1198-e1204.*

The publications are referred to in the text by their Roman numerals and are reprinted here with the permission of the publishers.

In addition, some unpublished data are presented.

Introduction

Esophageal atresia (EA) is a relatively common congenital malformation including a blind upper esophageal pouch with or without a connection to the trachea via a tracheoesophageal fistula (TEF). It affects one in 2500 to 3000 births. Without any treatment, EA is fatal. In fact, pediatric surgery was founded around surgery for infants with EA. The survival with EA has dramatically improved since the beginning of its successful surgical treatment, being nowadays well over 90% in dedicated centers (Goyal 2006). Today, even most infants with very low birth weight and severe cardiac malformations survive, due to improvements in surgery and in modern intensive care.

It is commonly accepted that gastroesophageal problems such as gastroesophageal reflux (GER) with its complications frequently occur after EA repair (Orringer 1977, Chetcuti 1988, Tovar 1995, Krug 1999, Tomaselli 2002, Deurloo 2003 and 2008, Konkin 2003, Little 2003, Taylor 2007). Although these complications are well characterized in infancy and in childhood, only a few studies with relatively small sample sizes involve the long-term outcome of EA, and none of these are population-based.

Reports on esophageal cancer among young adults with repaired EA (LaQuaglia 1987, Adzick 1989, Deurloo 2001, Pultrum 2005, Alfaro 2005, Taylor 2007) arouse concern about risk for esophageal cancer after repair of EA, and the necessity of long-term surveillance beyond childhood. Reflux esophagitis and esophageal columnar metaplasia are typical findings among EA patients, and are risk factors for esophageal adenocarcinoma. No studies exist on cancer after EA repair, and incidence of cancer among adults with repaired EA is unknown.

In addition to gastroesophageal sequlae, respiratory problems are also common in children and adolescents with EA and TEF (Chetcuti 1988, and 1993, Kovesi 2004, Malmström 2008). Approximately 10 to 20% have severe tracheobronchomalacia with airway instability and collapse (Spitz 1993, Goyal 2006). Recurrent respiratory infections, persistent cough, and wheeze are typical symptoms in childhood (Chetcuti 1993) and in adolescence (Malmström 2008), with a tendency to improve with age. However, repeated infections, aspiration, and persistent TEF may result in irreversible lung damage with bronchiectasis and chronic pulmonary disease. Although such respiratory problems are common in children and adolescents, long-term outcomes beyond childhood are unknown.

Reported incidences of vertebral and other skeletal anomalies in association with EA range from 9 to 24% (Engum 1995, Sparey 2000, Spitz 2006, Keckler 2007). Occurrence of musculoskeletal defects and scoliosis due to thoracotomy are even more common (Chetcuti 1989, Vanamo 1996). Many of the skeletal and hand anomalies are not evident in infancy and in childhood, and therefore their real incidence and natural history are unclear.

Patients with repaired EA have significant gastroesophageal (Biller 1987, Chetcuti 1988, Krug 1999, Deurloo 2003, Taylor 2007), respiratory (Biller 1987, Chetcuti 1988, Kovesi 2004, Taylor 2007, Lilja 2008), and musculoskeletal problems beyond childhood (Chetcuti 1988-1993). There exist no population-based studies with unselected patient series concerning long-term outcomes of EA, and pediatric surgeons rarely treat or meet these patients in adulthood.

Review of the literature

BACKGROUND

The first clearly documented case of a typical esophageal atresia with distal fistula was recorded by Thomas Gibson (1703) in 1697: "About November 1696, I was sent to an infant that would not swallow. The child seemed very desirous of food, and took what was offered it in a spoon with greediness; but when it went to swallow it, it was liked to be choked, and what should have gone down returned by the mouth and nose, and it fell into a struggling convulsive sort of fit upon it."

Timothy Holmes (London, UK) suggested surgical treatment for EA as early as in 1869. But Richter (1913), in Chicago, in the USA, was the first to describe a surgical technique: ligation of the TEF and end-to-end anastomosis of the esophagus (Harmon 2006, Spitz 2007). Thomas Lanman (1940), in Boston, in the USA, performed an extrapleural repair in 1936, but his patient lived for only three hours. The first survivors of a staged repair with a primary gastrostoma and a delayed esophageal reconstruction, were reported separately by Logan Leven (1941) (Minnesota, USA), and William Ladd (1944) (Boston) in 1939. Imperatori (1939) performed for the first time ligation of an isolated TEF transtracheally. Before that, EA had been uniformly fatal.

Cameron Haight (1943) was the first to perform a successful primary repair in 1941. Thereafter, reports came from different parts of the United Kingdom by Franklin (Hammersmith Hospital, London) in 1947, Sir Denis Browne (Great Ormond Street, London) in 1948, and Peter Paul Rickham (Liverpool) in 1949 (Spitz 1996). In Finland, Matti Sulamaa (1951) performed the first successful primary repair in February 1949.

In a case of a long gap EA, several lengthening techniques have been described such as mobilization of the fundus of the ventricle (Sweet 1948), elongation of the esophageal upper pouch with a bouginage (Howard and Myers 1965), bridging of the esophageal gap by introducing a silver prosthesis to which both esophageal segments were attached (Rehbein 1971), waiting for spontaneous growth of the esophageal segments (Puri 1981), a suture fistula technique (Shafer 1974, Schullinger 1982), circular myotomy of the esophagus to enable anastomosis (Livaditis 1973), and traction sutures (Foker 2005).

Since its early days, survival has improved along with improved surgical treatment, and modern intensive care. Esophageal repair with minimally invasive thoracoscopic repair was accomplished for the first time by Tom Lobe and Steve Rothenberg in North America (Lobe 1999), and Bax and van Der Zee in the Netherlands (Bax 2002).

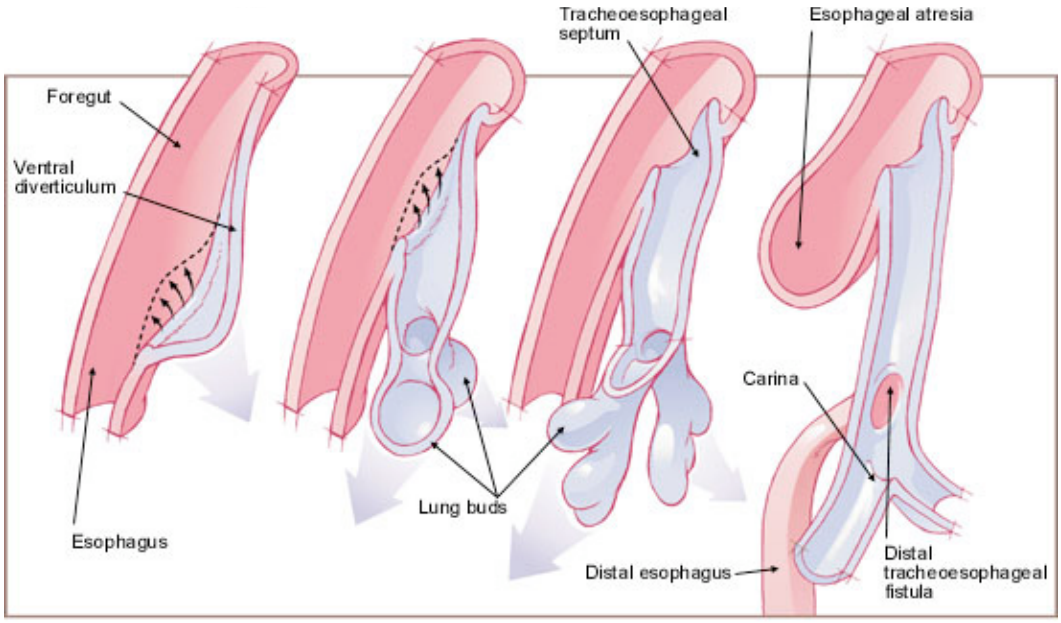

Figure 1 *Development of trachea and esophagus from a common foregut in embryology of esophageal atresia*

EMBRYOLOGY

In an early embryo, cells are located in three germ layers: ectoderm, mesoderm, and endoderm. The endodermal layer is converted into the primitive gut tube, from which the airways and the esophagus are derived. The trachea and esophagus develop from the common primitive foregut (Figure 1) as the developing respiratory and digestive tubes are separating by lateral ingrowth of epithelial ridges from four weeks of gestation (Ioannides 2009). Defects of mesenchymal proliferation during this critical process have been implicated in the pathoembryogenesis of EA-TEF. In 1978, Thompson described a number of malformations, including EA/TEF, in rat and rabbit fetuses exposed in utero to the anticancer agent Adriamycin (doxorubicin hydrochloride). An Adriamycin rodent model, created by Diez Pardo in 1996, has given us deeper understanding of EA-TEF and other VACTERL anomalies. Sonic hedgehog (Shh) is implicated in vertebrate axial organogenesis that appears to be essential to foregut development and differentiation. Defects in Shh gene expression result in abnormal tracheoesophageal separation in the Adriamycin model (Ioannides 2003), Shh signalling pathway defects in the VACTERL phenotype (Kim 2001, Spilde 2003), and targeted Shh deletion in EA-TEF anomalies in mice (Litingtung 1998).

EPIDEMIOLOGY

EA occurs in one of every 2500 to 3000 live births (Louhimo 1983, Spitz 2007) with a slight male preponderance (59%) (Höllwarth 2006). The majority of cases are sporadic or non-syndromatic, and only a small number are associated with chromosomal abnormalities. Familial or syndromic cases are extremely rare (less than 1%). The incidence in twins is 2- to 3-fold that of the general population (Orford 2000).

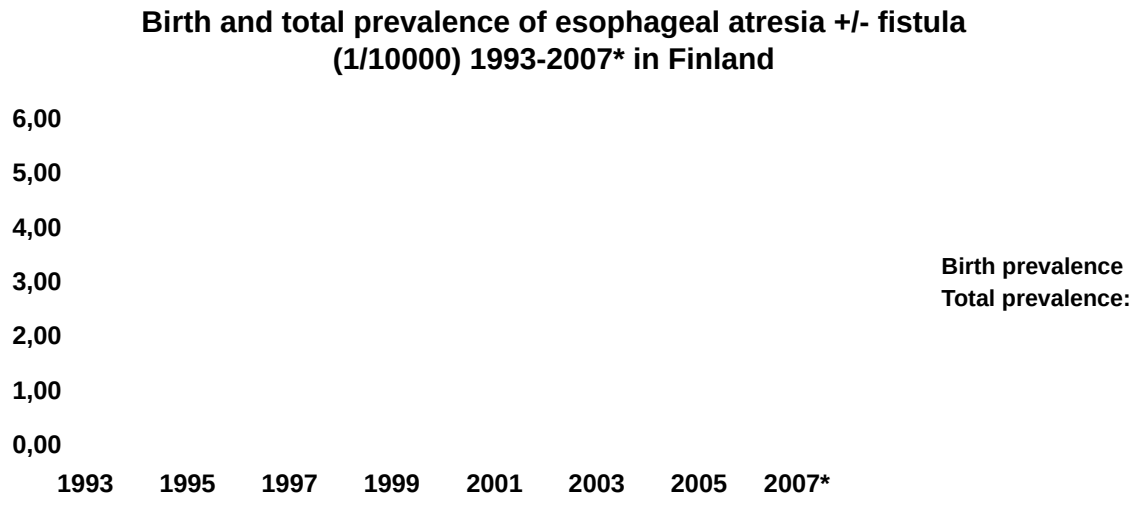

Figure 2 *Birth prevalence of EA between 1993 and 2007 in Finland (personal communication with Ritvanen 1/2010, Finnish National Institute for Health and Welfare)*

In Finland, the incidence between 1993 and 2007 was one in 2840 live births (Figure 2) with a male preponderance (57%). Maternal age was in relation to prevalence of EA (Figure 3). Prevalence in twins was 7.8%, in cromosome abnormalities 13%, in genetic diseases 1.2%, and relating to syndromes 69%, between 1993 and 2007 in Finland (personal communication with Ritvanen 1/2010, Finnish National Institute for Health and Welfare).

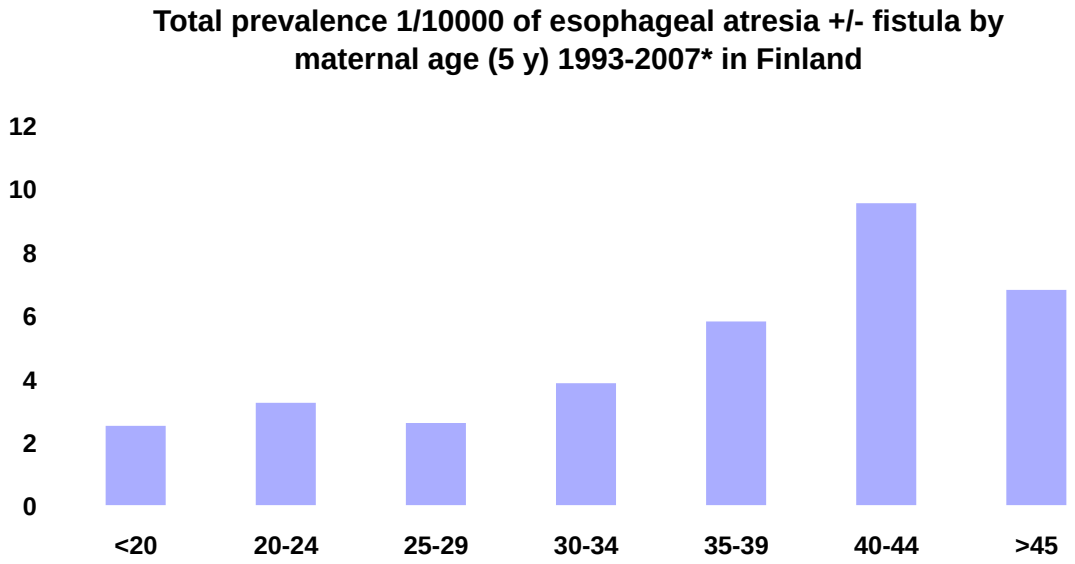

Figure 3 *Maternal age in relation to prevalence of EA between 1993 and 2007 in Finland (personal communication with Ritvanen 1/2010, Finnish National Institute for Health and Welfare)*

ASSOCIATED ANOMALIES

Early disturbance in organogenesis resulting in EA deformities often affects other organ systems. Over half the patients with EA have associated anomalies (Harmon 2006, Spitz 2006 and 2007). Most commonly affected are the cardiovascular system in 29 to 32% (Greenwood 1976, Chittmittrapap 1989, Keckler 2007), the genitourinary system in 24% (Beasley 1992), the anorectum in 13%, and some other part of the gastrointestinal tract in 14% (Chittmittrapap 1989, Keckler 2007). At least 18 different syndromes have been reported in association with EA (Höllwarth 2006). The *VATER* association (Quan 1973) or the *VACTERL* multianomaly association (Temtamy 1974) with **v**ertebral, **a**norectal, **c**ardiac, **t**racheo-**e**sophageal, **r**enal, and **l**imb defects, is relatively common with an occurrence of 20% (Lilja 2008, de Jong 2008, Harmon 2006). Other midline defects (cleft lip and palate, sacral dysgenesis, and urogenital anomalies), chromosomal anomalies (18 trisomies, and 21 trisomies), and the *CHARGE* association (Pagon 1981) with **c**oloboma, **h**eart defects, **a**tresia of choanae, **r**etarded development, **g**enital hypoplasia, and **e**ar abnormalities relating to EA, are more rare (Harmon 2006). Some rare syndromes and one-gene defects are always associated with EA.

Associated neurological anomalies include neural tube defects, hydrocephalus, holoprosencephaly, and anophthalmia or microphthalmos. Other anomalies include abdominal wall defects and diaphragmatic hernia. Incidence of certain associated anomalies may vary by world region, and the type of EA. Associated anomalies are most common in cases of EA without TEF, and are least common in cases of isolated, meaning H-type TEF (Harmon 2006, Spitz 2007).

Cardiac defects account for most of the deaths associated with EA malformations. The most common single defects identified are ventricular septal defect (VSD) (19%) and atrial septal defect (ASD) (20%). Other common cardiac anomalies include the tetralogy of Fallot (5%) and patent ductus arteriosus (13%). Rare cardiac anomalies associated with EA are coarctation of the aorta in 1 to 4%, and right-sided aortic arch in 4% (Deurloo 2002).

Gastrointestinal anomalies that associate with EA include anorectal malformations (14%), duodenal atresia (2%) (Deurloo 2002), intestinal malrotation (4%) (Cieri 1999), ileal atresia, annular pancreas, and pyloric stenosis. Genitourinary defects include renal agenesis or hypoplasia (1%), hypospadias, undescended testis, cystic renal disease, hydronephrosis, vesicoureteral reflux, ureteric duplication, pelvic ureteral and vesicoureteral obstruction, urachal anomalies, ambiguous genitalia, and cloacal or bladder extrophy (Beasley 1992, Cord-Udy 1996, Harris 1995).

Typical musculoskeletal anomalies include limb defects in 15 to 16% and vertebral anomalies in 17 to 24% (Harmon 2006, Keckler 2007). Typical limb anomalies are radial ray anomalies varying from thenar aplasias or hypoplasias to floating thumbs or absent thumbs. Other musculoskeletal defects such as scoliosis and chest defects are also related to EA (Chetcuti 1989). Many of the skeletal anomalies and defects may become evident as the child grows.

Gross 1953	A	B	C	D	E	F
Incidence (%)	7	1	86	2	4	-
Vogt 1929	2	3a	3b	3c	4	-
Ladd 1944	I	II	III, IV	V	-	-

Gross A Isolated esophageal atresia (EA)
Gross B EA with proximal tracheoesophageal fistula (TEF)
Gross C EA with distal TEF
Gross D EA with double TEF
Gross E Only TEF
Gross F Esophageal stenosis

Figure 4 *Classifications of esophageal atresia by Vogt (1929), Ladd (1944), and Gross (1953) with their incidences (Spitz 2007)*

CLASSIFICATION

Over the years EA has been classified by anatomy (Vogt 1929, Ladd 1944, Gross 1953) and by clinical prognostic factors for survival (Waterston 1962, Spitz 1994) (Figure 4). The Waterston classification is based on birth weight, pneumonia, and associated anomalies (Table 1), and the Spitz classification on birth weight and associated cardiac anomalies (Table 2). Despite the progress made in the last 50 years, the Waterston classification still has prognostic relevance (Deurloo 2004).

Table 1. *Waterston (1962) risk groups and survival figures (Spitz 2007)*

Group	Survival (%)	Waterston classification
A	100	Birth weight >2500 g and otherwise healthy
B	85	Birth weight 2000 – 2500 g and well **or** higher weight with moderate associated anomalies (noncardiac anomalies plus PDA, VSD, or ASD)
C	65	Birth weight <2000 g or higher **with** severe associated cardiac anomalies

PDA – patent ductus arteriosus, VSD – ventricular septal defect, and ASD – atrial septal defect

Table 2. *Spitz classification of esophageal atresia (1994) according to predictors of survival with their published rate of survival*

Group	Survival (%)	Birth weight (gr) and major cardiac anomalies
I	97	>1500 with no cardiac anomalies
II	59	<1500 or cardiac anomaly
III	22	<1500 and cardiac anomaly

DIAGNOSIS

Prenatal diagnosis of EA is rare but possible by ultrasonography showing absence of a stomach bubble and maternal polyhydramnion (Harmon 2006, Hutson 2008). Polyhydramnion is a non-specific manifestation of fetal swallowing disorders or fluid passage through the uppermost part of the fetal intestinal tract (Höllwarth 2006). EA should be recognized as soon as possible after birth, as delay may lead to aspiration and pulmonary complications. Typical symptoms include excessive salivation, regurgitation, choking and coughing after the first feeding resulting in cyanosis and respiratory distress (Harmon 2006, Hutson 2008). Inability to pass a catheter through the mouth or nose into the stomach suggests EA, and the diagnosis is ascertained with a plain chest radiograph demonstrating the nasogastric tube in the blind upper pouch of the esophagus (Harmon 2006, Hutson 2008). Atresia type must be determined prior to surgery. Air below the diaphragm on a plain radiograph including neck, chest, and abdomen provides evidence of a lower tracheoesophageal fistula; in contrast, a gasless abdomen indicates a pure EA, and an expected long distance between the segments (Höllwarth 2006). In cases of H-type fistula, diagnosis is commonly delayed, and suspected only after recurrent respiratory infections, and coughing and choking during feedings. The diagnosis is ascertained with dynamic prone video esophagography and bronchoscopy (Brookes 2007).

Every neonate with EA needs to be examined for visible anomalies such as anal atresia or limb anomalies. Screening for associated malformations includes a plain radiograph of the chest and abdomen (cardiac defects, diaphragmatic hernia, intestinal atresia, skeletal/vertebral anomalies, congenital scoliosis), ultrasonography (brain/neurological, kidneys), and echocardiac evaluation (cardiac defects, right-sided aortic arch). Karyotyping is also performed to detect chromosomal defects, especially trisomy 18 or trisomy 21 (Down´s syndrome). (Harmon 2006, Hutson 2008.)

PREOPERATIVE TREATMENT

After diagnosis, the infant is positioned in a supine position with the head of the bed elevated (i. e. anti-Trendelenburg´s position) with low-pressure suction applied to the upper pouch of the esophagus to minimize risk for aspiration pneumonitis. The infant receives broad-spectrum antibiotic treatment and intravenous fluid therapy, and vitamin K is administered before surgery. (Harmon 2006, Hutson 2008.)

SURGERY

Surgical treatment depends on anomaly type. The most common type of EA, with an incidence of 86% (Spitz 2007), is atresia with distal fistula, which is repaired through a right posterolateral thoracotomy by *fistula ligation and primary esophageal anastomosis* (Harmon 2006, Hutson 2008) (Figure 5). The repair may be either extrapleural or transpleural. The appropriate site for the incision is between the fourth and fifth ribs.

In cases of long-gap atresia, *esophageal lengthening techniques* with circular myotomy by Livaditis (1973) or with traction sutures as described by Foker (2005) may enable end to end anastomosis. This usually results in an anastomosis under tension. Due to the long distance between esophageal pouches, cases of EA without fistula are usually treated by *staged repair* with primary formation of a gastrostomy for feeding and continuous suctioning, or of a neck fistula of the blind upper pouch of the esophagus to protect the airway. Delayed repair is performed several weeks or a few months later with native esophagus when possible. Otherwise, *esophageal replacement* with gastric tube esophagoplasty, gastric interposition, jejunal interposition, or colonic interposition is required. These methods carry a high risk for complications and high morbidity rates (Lindahl 1990, Lindahl 1995, MacCollum 2003).

The isolated H-type fistula is surgically closed through the neck by a cervical approach, or by broncoscopy with laser, electrocauter, and histoacryl glue (Tzifa 2006). In some cases, a right-sided thoracotomy is required.

Even though minimally invasive *thoracoscopic techniques* for EA repair have been established, they may carry a higher potential for complications such as esophageal anastomotic leak, esophageal stricture, and recurrent TEF (Goyal 2006, Holcomb 2005, Lima 2007, Rothenberg 2005).

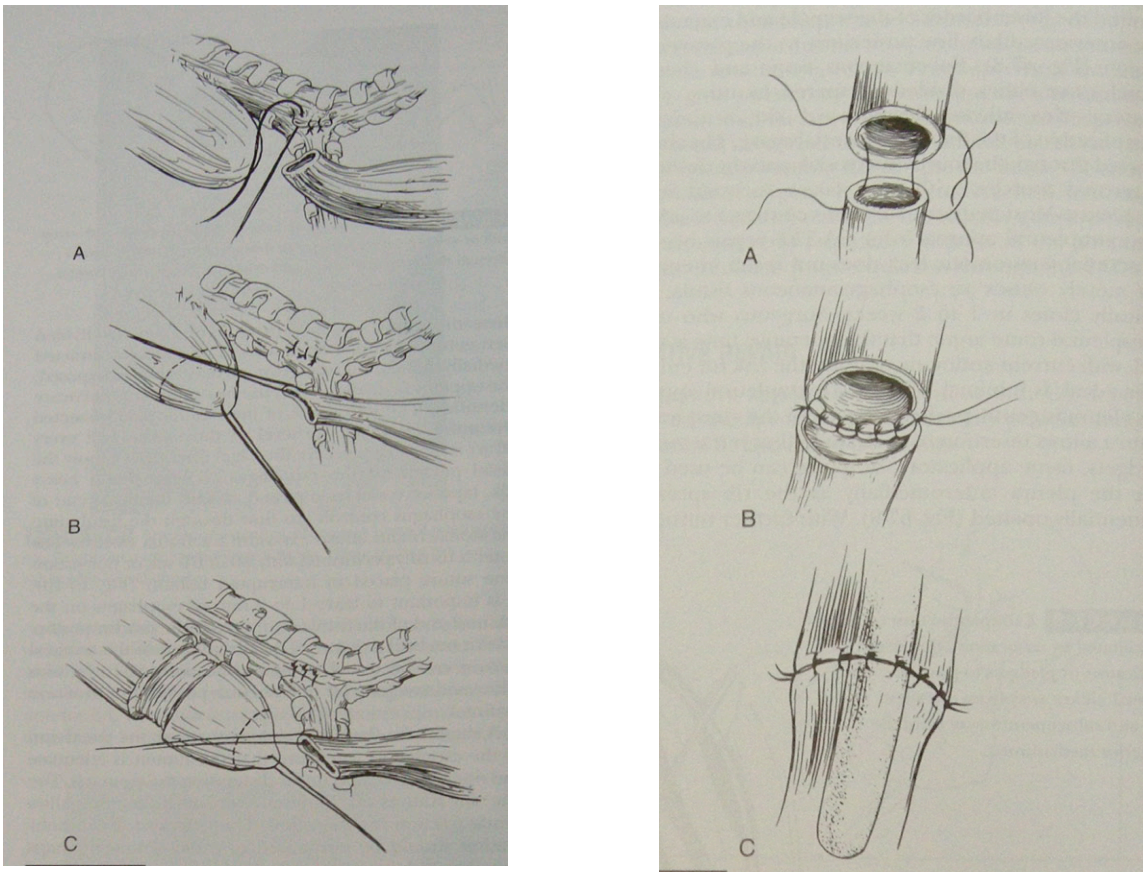

Figure 5 *Closure of the tracheoesophageal fistula (A), mobilization with traction sutures (B), and circular myotomy to enable esophageal anastomosis (C). Creation of esophageal end-to-end anastomosis with single layer sutures (A-C)*

OUTCOMES

Survival

Overall survival after EA at the time of discharge in dedicated centers is now well over 90% (Konkin 2003, Goyal 2006, Keckler 2007). The Spitz classification system based on birth weight and cardiac malformations appears to provide the most accurate prognosis (Konkin 2003, Spitz 1994-2007). Although VACTERL anomalies are common in patients with EA, they appear to have little impact on overall survival (Keckler 2007). In the past, mortality was mainly due to low birth weight or prematurity, cardiac defects, multiple associated anomalies, and respiratory complications.

In the Hospital for Children and Adolescents, Helsinki University, Finland, mortality after EA has markedly decreased over the last decades (Table 3). In the early years, high mortality was associated with failure of surgical treatment, pneumonia, problems related to prematurity, and trisomies 18 and 21 with multiple anomalies. More recently, the main causes of death have been prematurity with low birth weight and trisomies 18 and 21 with major cardiac defects. Nowadays, nearly all patients will survive.

Table 3. *Numbers of patients undergoing surgery for esophageal atresia and percentages discharged from hospital alive by year of operation in the Hospital for Children and Adolescents, Helsinki University, Finland, according to Louhimo (1983), my own work and personal communication (Pakarinen and Koivusalo 9/2009)*

Time-period	Number of patients	Survival (%)
1947 – 1956	100	19
1956 – 1960	100	43
1960 – 1965	101	56
1965 – 1971	101	70
1971 – 1978	100	85
1978 – 1985	86	85
1989 – 2007	89	97

Postoperative complications and their management

Typical early complications following EA repair include esophageal anastomotic leak, esophageal stricture, and recurrent TEF, as well as pneumonia and tracheomalacia (Mortell 2009, Harmon 2006, Kovesi 2004, Louhimo 1983) (Table 4). Late complications such as GER, dysphagia, esophageal stenosis, recurrent TEF, esophageal dysmotility, and esophageal epithelial changes, as well as respiratory morbidity and functional impairments, and musculoskeletal defects (Kovesi 2004, Goyal 2006, Rintala 2009) may occur later in life. Surgery, in addition to associated musculoskeletal anomalies, may contribute to anterior chest wall deformities, scapular winging, and scoliosis, and it may interfere with normal female breast development to an extent that may require plastic surgical repair later (Cherup 1986, Chetcuti 1989, Vanamo 1996).

Esophageal anastomotic leak may require re-thoracotomy, lavage, and suturing. For minor leaks, conservative treatment with drainage and antimicrobic treatment is sufficient. Most of the esophageal anastomotic strictures are treated with repeated endoscopic dilatations. Any stricture that fails to respond to endoscopic dilatations requires a stricture resection and creation of a new anastomosis. Recurrent fistulas are treated with broncoscopy and lasering, and sometimes with re-thoracotomy and re-ligation. Acute life-threatening events with recurrent aspiration and apneas associated with tracheobronchomalacia are treated with *aortopexy*, with or without *fundoplication*. Severe GER, recurrent strictures, and life-threatening events with aspiration and apneas are the main indications for antireflux surgery with fundoplication. However, figures for the incidence of antireflux surgery show a wide range (from 3 to 52%) (Biller 2987, Holcomb 2005, Deurloo 2005, Kawahara 2007).

Table 4. *Early anastomotic complications following esophageal atresia repair*

Reference	Years	N	Anastomotic leak	Anastomotic stricture resection	Recurrent fistula
Louhimo 1983	1947 – 1976	500	13%	1%	5%
Manning 1986	1977 – 1985	63	17%	4%	6%
Spitz 1987	1980 – 1984	148	21%	3%	12%
Randolph 1989	1982 – 1988	39	10%	5%	5%
Engum 1995	1971 – 1993	174	NR	1%	2%
Yanchar 2001	1989 – 1999	90	17%	NR	3%
Holcomb 2005	1999 – 2005	104	8%	2%	2%
Lilja 2008	1986 – 2005	147	7%	NR	8%
Mortell 2009	1997 – 2007	70	7%	3%	7%

NR – not reported

Esophageal morbidity

Late clinical symptoms and complications of esophageal anastomosis

EA is often associated with various esophageal symptoms: regurgitation, heartburn, aspiration, and dysphagia (Engum 1995, Somppi 1998, Chetcuti 1993). Incidence of dysphagia ranges from 39 to 77%, and GER from 17 to 63% (Orringer 1977, Chetcuti 1988, Tovar 1995, Krug 1999, Tomaselli 2002, Deurloo 2003 and 2008, Konkin 2003, Little 2003, Taylor 2007). Most of these studies involved children and adolescents, not adults. Typical late complications of the esophageal anastomosis are esophageal stricture in 30 to 56% and recurrent TEF in 5 to 14% (Engum 1995, Konkin 2003, Kovesi 2004, Spitz 2007, Lilja 2008). Strictures are more common in patients with long-gap atresia (Kovesi 2004). Persistent strictures are often associated with GER (Chittmittrapap 1990) and thus require prompt antireflux treatment with fundoplication in addition to dilatations or stricture resection or both.

Esophageal motility

EA is associated with esophageal dysmotility: low esophageal distal wave amplitudes and non-propagating peristalsis of the esophagus (Orringer 1977, Tovar 1995, Tomaselli 2002, Kawahara 2007). A total of 35% have delayed gastric emptying, and 45% altered gastric peristaltic activity (Romeo 2000). Esophageal dysmotility together with altered anatomy of the gastroesophageal junction may result in GER, esophagitis, esophageal epithelial metaplasia, and even esophageal cancer (LaQuaglia 1987, Adzick 1988, Deurloo 2001, Alfaro 2005, Pultrum 2005, Taylor 2007). Lack of distal esophageal contractions correlates with the development of GER ($P<0.001$) (Kawahara 2007), and patients reporting dysphagia often will have more disturbed motility ($P=0.011$) and lower scores for quality of life (Deurloo 2008).

Esophageal epithelial changes

Esophageal dysmotility predisposes to GER, which may give rise to esophageal epithelial changes: esophagitis, and esophageal columnar metaplasia without goblet cells (gastric metaplasia) or with goblet cells (intestinal metaplasia, i. e., Barrett´s esophagus). Incidence of histological esophagitis among EA patients has been reported in approximately 64%, and Barrett´s in 7% (Biller 1987, Krug 1999, Deurloo 2003 and 2005, Taylor 2007) (Table 5). Most of these studies included only symptomatic patients, however. To date, reported cases of esophageal cancer among adults with repaired EA have numbered only six (Table 6).

Table 5. *Incidence of gastroesophageal reflux symptoms and histologically proven esophagitis and Barrett´s esophagus in endoscopic long-term follow-up studies*

Reference	Age (years) (mean)	GER symptoms	Esophagitis	Barrett´s
Biller 1987	22 – 31 (26)	9/12	4/12	1/12
Krug 1999	18 – 26 (22)	13/39	9/17	2/17
Deurloo 2003	28 – 45 (34)	15/40	19/21	1/21
Deurloo 2005	10 – 26 (17)	23/86	30/40	0/40
Taylor 2007	20 – 48 (33)	63/83	36/62	7/62
Total	10 – 48	123/260 (47%)	98/152 (64%)	11/152 (7%)

Table 6. *The six reported cases of esophageal cancer after repair of esophageal atresia*

Reference	Age (years)	Gender	Histology
LaQuaglia 1987	44	Female	Squamous cell carcinoma
Adzick 1989	20	Female	Adenocarcinoma
Deurloo 2001	38	Male	Squamous cell carcinoma
Pultrum 2005	22	Female	Adenocarcinoma
Alfaro 2005	46	Female	Adenocarcinoma
Taylor 2007	44	Not reported	Squamous cell carcinoma

Epidemiology of esophageal cancer

In the absence of a hiatal hernia, the tubular esophagus joins the stomach at the level of the diaphragmatic pinch, above which the squamo-columnar epithelial junction is located (Lambert 2007). Barrett's esophagus is defined as a replacement (metaplasia) of the normal esophageal squamous mucosa with columnar epithelium that contains goblet cells most commonly arising in the setting of chronic GER with repeated mucosal injury (Schuchert 2007). Columnar metaplasia is a preneoplastic condition, but the requirement of intestinal metaplasia (goblet cells) for the neoplastic potential to develop is unknown (Lambert 2007). Columnar metaplasia predisposes to development of mucosal dysplasia and ultimately to adenocarcinoma, with a 50- to 100-fold increased cancer risk compared to that of the general population (Schuchert 2007), which corresponds to a 0.5% annual risk for cancer (Voutilainen 1999). In general population studies, the prevalence of Barrett´s esophagus is approximately 1.6% (Ronkainen 2005).

Although previous studies lack strict evidence supporting surveillance, surveillance endoscopies are recommended at 3- to 5-year intervals for Barrett's esophagus even without dysplasia, with biopsy sampling from any Barrett's epithelium to evaluate any appearance of dysplastic changes. Surveillance endoscopies are recommended at one-year intervals with low-grade-dysplasia, and with three-to-six month intervals with high-grade-dysplasia. Esophageal dysplasia can be treated with endoscopic ablation, photodynamic therapy, or endoscopic mucosa resection. Esophagectomy and replacement result in high morbidity and impaired quality of life. No antireflux therapy promotes the regression or prevents progression of Barrett´s metaplasia or reduces the risk for esophageal adenocarcinoma. (Schuchert 2007.)

Adenocarcinoma (ADC) of the esophagus develops in the columnar lining of the esophagus, when squamous cell cancer (SCC) of the esophagus is linked to *alcohol and tobacco consumption* in Western countries. Preneoplastic conditions include *columnar lined esophagus as a complication of GER*, and *erosive esophagitis in alcoholics*. Factors that cause inflammation of the esophageal mucosa (bile and acidic reflux) and deregulation of cell cycle and apoptosis (for example TP53 gene mutations) predispose to metaplastic alterations. Columnar metaplasia develops in the distal esophagus after destruction of the squamous epithelium by bile and acid stress. Higher risk is associated with male sex, old age, alcohol consumption, continuous smoking, insufficiency of dietary fruit and vedgetables, and prolonged reflux symptoms. (Lambert 2007.)

Histological esophageal columnar metaplasia may be further evaluated with IHC for CDX2 and MUC2. The CDX2 gene is an intestinal transcription factor that may be involved in regulation of the proliferation and differentation of intestinal epithelial cells (Eda 2003). The CDX2 protein codes mucines such as the mucus-secreting goblet cell-mucin marker MUC2. CDX2 and MUC2 are expressed in the healthy intestinal mucosa, but not in the healthy epithelium of the esophagus and stomach. They are also expressed in the intestinal metaplasia of the esophagus, i. e., as Barret´s esophagus. Expression of CDX2 may be an early event leading to the development of Barrett´s esophagus (Eda 2003). In mice, gastric expression of CDX2 alone is sufficient to induce intestinal metaplasia (Silberg 2002). Nuclear staining for CDX2 in non-goblet columnar epithelial cells indicates their intestinal differentation, and they are suggested as the precursor of an equivocal Barrett´s mucosa and would allow its designation as early Barrett´s mucosa (Steininger 2005). CDX2 expression in cardiac-type mucosa might be able to detect undetected intestinal metaplasia in columnar-lined esophagus, and thus serve as a putative marker for intestinal metaplasia in the absence of goblet cells (Kerkhof 2006).

Respiratory morbidity

Symptoms

After repair of EA, respiratory problems are relatively common. Occurrence of respiratory symptoms ranges from 33 to 41% (Chetcuti 1988 and 1993, Somppi 1998, Taylor 2007, Malmström 2008). Typical respiratory symptoms associating with EA include aspiration, failure to thrive, choking, wheezing, persistent cough, repeated respiratory infections, and asthma (LeSouëf 1987, Chetcuti 1992 and 1993, Kovesi 2004, Malmström 2008). After 2 years' follow-up, 24% have experienced respiratory problems (Calisti 2004), and in adolescence at a mean age of 14 years, 41% have had respiratory symptoms (Malmström 2008). Wheeze occurs in approximately 37% of the survivors of EA with no tendency toward improvement with age (Somppi 1998, Chetcuti 1993, Agrawal 1999, Goyal 2008). Prevalence of doctor-diagnosed asthma (DDA) during childhood and adolescence after repair of EA has been 12 to 29% (LeSouëf 1987, Somppi 1998, Agrawal 1999, Taylor 2007, Malmström 2008). This is higher than in the general population in children (8.8%) (Malmström 2008), and in adults (6%) (Pallasaho 2002). In the few adult studies on EA patients, 33% had respiratory symptoms (Chetcuti 1988, Taylor 2007), and restriction was the main ventilatory defect (Biller 1987, Chetcuti 1988).

Aspiration resulting from GER or from recurrent TEF in association with EA may predispose to cough, choking, and respiratory infections. With time, and when untreated, these can result in chronic irreversible pulmonary diseases with airway damage and reduced lung volume. A strong connection exists between severity of GER and persistence of respiratory symptoms among EA survivors (Goyal 2008). Recurrent chest infections such as bronchitis and pneumonia occur in up to two-thirds of the survivors in the early years of life, but respiratory morbidity decreases in frequency and severity as the child reaches late adolescence (Chetcuti 1993). Tracheomalacia with typical harsh barking cough and wheezing occur in 10 to 20% of infants with repaired EA (Goyal 2008). Aortopexy prevents further life-threatening apneas in severe tracheal instability associated with EA. An increased susceptibility to respiratory infections has been observed in childhood (Vazquez-Jimenez 2001). Isolated H-type TEF is often associated with delayed diagnosis with typical symptoms that include coughing with feedings, recurrent pneumonia, and episodic cyanosis (Brookes 2007).

Pulmonary function

Of children and adolescents with repaired EA, restrictive PF occurs in 21 to 40%, and obstructive PF in 12 to 54% (Milligan 1979, Chetcuti 1992, Robertson 1995, Malmström 2008). The PF abnormalities do not correlate with current respiratory or esophageal symptoms. The reason for PF abnormalities is unclear, but it has been suggested that they are caused by permanent lung damage from recurrent aspiration in the patients' early years (Chetcuti 1992), by poor tracheal clearance leading to recurrent episodes of bronchitis or pneumonia leading to lung damage (LeSouëf 1987, Robertson 1995), or by poor lung growth during infancy (Milligan 1979).

Prevalence of bronchial hyper-responsiveness (BHR) in a general healthy population with normal lung volumes was 17% (Juusela 2008). Increased bronchial responsiveness has been described in 36% of EA patients with TEF (Table 5), reflecting sequalae of chronic lung disease from damaged epithelium in the airways (Milligan 1979). Severe or moderate BHR is associated with a more restrictive ventilatory defect (Malmström 2008). No correlation has emerged between increased BHR and history of DDA or atopic eczema (Robertson 1995, Malmström 2008).

Exhaled nitric oxide level (FE^{NO}) is associated with the eosinophilic airway inflammation that is increased particularly in patients with atopic asthma, and it is steroid responsive (Taylor 2006). Levels of FE^{NO} were elevated in 23% of the adolescents with repaired EA and were detectable only in patients with atopy and increased BHR. However, FE^{NO} did not correlate with the respiratory symptoms (Malmström 2008).

Musculoskeletal defects

Deformities of the chest wall and spine may result from associated vertebral and skeletal anomalies, or be due to thoracotomy. One study reported that 24% of children with repaired EA have “winged” scapula, and 20% anterior chest wall deformities (Jaureguizar 1985). Another report noted rib fusion and female breast deformities (Cherup 1986). A third report supports these findings with a 20% occurrence of anterior chest wall deformities after EA repair (Chetcuti 1988). Shoulder asymmetry, “winged” scapula, and limited motion of the right upper extremity result from paralysis of the latissimus dorsi muscle, and chest wall deformities from atrophy of the serratus anterior muscle, thoracotomy-indused rib fusions, scoliosis, or other deformities of the thoracic cage (pectus carinatum or excavatum). In VACTERL multianomaly syndrome, in addition to vertebral anomalies, various limb anomalies occur, especially in the region of the radial ray. The long-term morbidity and functional impairments of these defects remain unclear, however.

Quality of life

At a median age of 38 years, adults with repaired EA achieve a gastrointestinal quality of life index (GIQLI) score similar to that of their general population-derived controls, even though they have more dysphagia and GER ($P<0.05$) and a lower respiratory symptom-related quality of life index (RSRQLI) ($P<0.05$). No difference, however, in health-related quality of life (P=ns) (Koivusalo 2005) appeared. One-third of the adult survivors (follow-up time 16 years or more) have had negative effects of EA on their daily life, especially dysphagia, but their generic quality of life, as well as physical and mental health, was good (Deurloo 2005). Patients reporting dysphagia more often had disturbed motility ($P=0.011$) and lower scores for quality of life (Deurloo 2008). In another study, the GIQLI results were similar after primary anastomosis for esophageal atresia to those of healthy controls (Ure 1998).

Aims

The objective of this study was to assess the long-term outcomes of esophageal atresia.

The specific aims were to evaluate

1) Cancer incidence (I)

2) Esophageal morbidity and function (II)

3) Respiratory morbidity (III)

4) Spinal abnormalities (IV)

in adults with repaired EA compared to the general population.

Patients and methods

PATIENTS AND CONTROLS

The hospital records of all 588 patients treated for EA at the Hospital for Children and Adolescents, Helsinki University Central Hospital, Finland, between 1947 and 1985 were completely reviewed. The data were retrospectively abstracted from the patient records by means of a standardized data extraction sheet concerning survival, type of EA, associated anomalies, surgical treatment, and complications. Vital status and postal address were traced from the database of the Population Register Center of Finland based on a personal identification code given to all residents in Finland.

Those 502 treated for EA between 1947 and 1978 were followed up for cancer (I) through the files of the National Cancer Registry. Between 1947 and 1985, a total of 588 infants were operated on for EA, of whom 296 were alive at the beginning of the study in November 2005; 34 patients with esophageal substitutes were excluded. Additionally, 16 patients had emigrated, and postal addresses of 11 patients remained unknown. The remaining 235 (90%) eligible survivors with their native esophagus were contacted by mail during 2005. The letters described the protocol and purpose of the study. Of the study population, the first 101 who returned their signed informed consent were invited to enter the study (Figure 6). The study on long-term outcomes of EA concerned esophageal morbidity (II), respiratory morbidity (III), and skeletal defects (IV). A symptom questionnaire also went to a group of general population-derived controls randomly chosen from the Population Register Center of Finland and matched for age, gender, and municipality of residence.

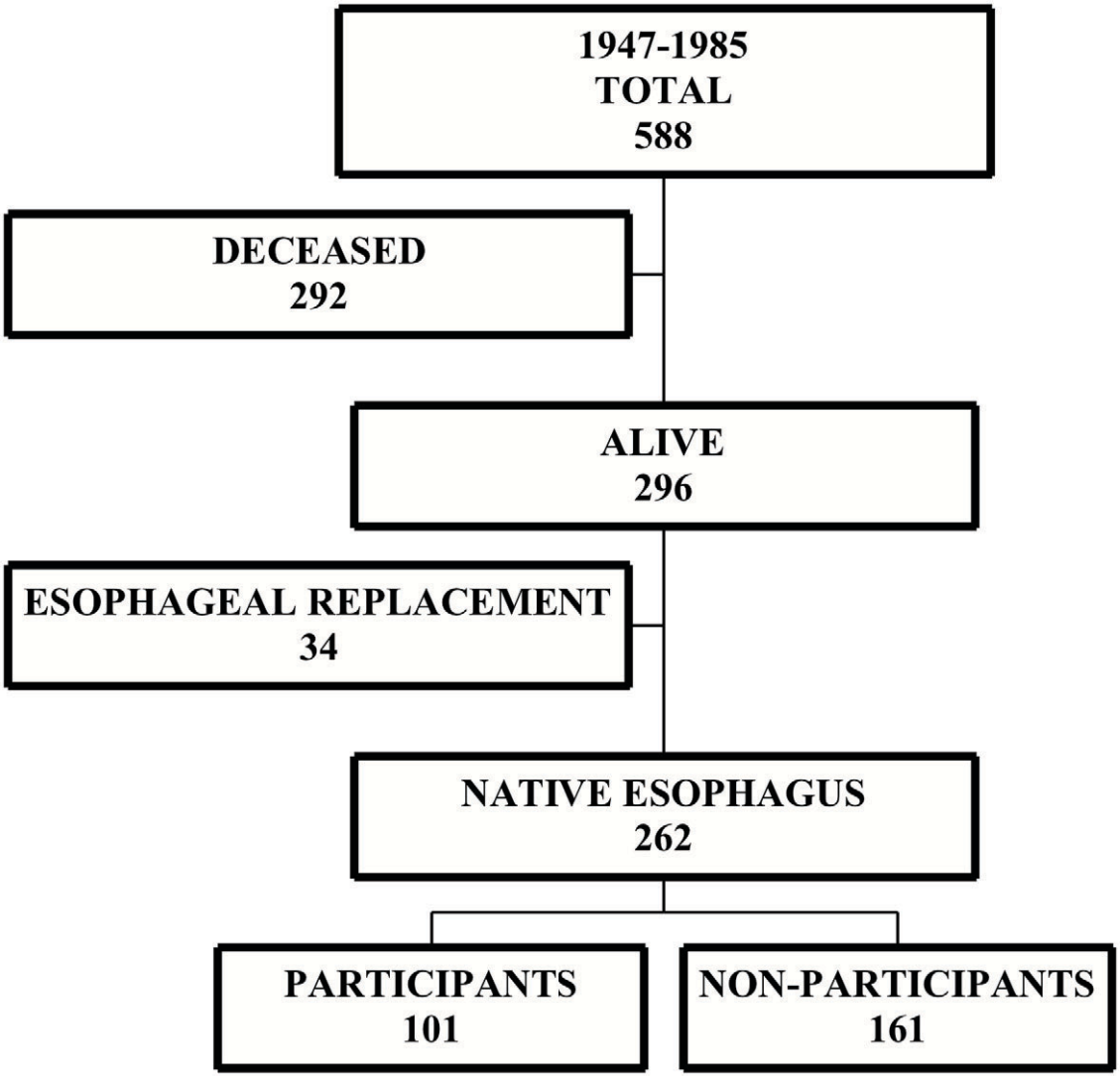

Figure 6 *Patients treated for esophageal atresia 1947-1985*

METHODS

Cancer (I)

A total of 502 consecutive patients treated for EA in our hospital from 1949 to 1978 were followed up for cancer through the files of the population-based countrywide cancer registry from 1967 to 2004. Follow-up for cancer was performed automatically based on a unique personal identification code in a linkage with the population-based countrywide Finnish Cancer Registry (Pukkala 1992, Teppo 1994). 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 (Finnish Cancer Registry). The standardized incidence ratios (SIRs) were the actual cases divided by the expected numbers.

Esophageal morbidity (II)

Esophageal symptoms

All patients were interviewed by means of validated questionnaires for the gastrointestinal quality of life index (GIQLI) (Eypasch 1995), and a gastrointestinal-symptom rating scale (GRS) (Svedlund 1988). Criteria for GER were frequent or constant heartburn, regurgitation, or intense burping (GIQLI), and from moderate to severe heartburn, regurgitation, or burping (GRS). Patients were classified as having no GER, symptomatic GER, medically treated GER, or surgically treated GER. Classification criteria for dysphagia were constant or frequent swallowing difficulties with frequent drinking accompanying eating, or careful chewing of the food, dysphagia leading to dietary limitations, and frequent esophageal food impactions with or without need for endoscopic foreign body removals. The GIQLI cut-off point was set at < 105 of a possible 140 points for definition of impaired gastrointestinal-related quality of life (Koivusalo 2005).

Esophageal function

All patients underwent esophago-gastro-duodenoscopy, and esophageal stationary pullthrough manometry (II). After their overnight fasting, they underwent endoscopy in the left lateral position without sedation, with a Pentax (EG-2985 K; Tokyo, Japan) endoscope. Routine biopsies were done in the proximal esophagus 20 cm from the incisor line, and the distal esophagus 2 cm above the esophagogastric junction. Additional biopsy specimens came from any mucosal lesions. Findings were recorded and lesions photographed. Esophagitis was scored as A, B, C, or D according to the Los Angeles (LA) classification (Armstrong 1996, Lundell 1999).

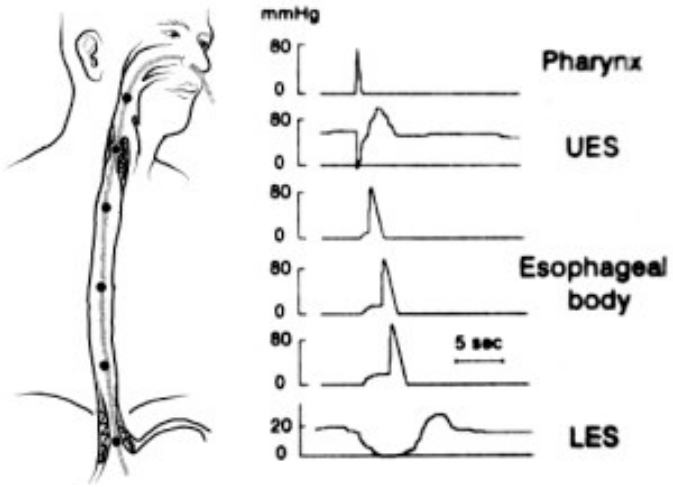

Figure 7 *Esophageal manometry waves at the site of the pharynx, upper esophageal sphincter (UES), esophageal body 15, 10, and 5 cm above the lower esophageal sphincter (LES), and the LES*

Manometry was performed as described previously (Richter 1987, Kahrilas 1988, Mittal 2004) with a lubricated transnasally placed eight-lumen standard manometric catheter (MedTronic Inc, Type 9012P1221, Minneapolis, MN, USA) with four radial openings 90° from each other at the same level, and the remaining four spaced 5 cm apart (Figure 7). The catheter was perfused with bubble-free distilled water at a constant rate of 0.6 mL/min with a low-compliance pneumohydraulic system (Mui Scientific, MS4-1361, model PIP-4-8, Mississauga, Ontario, Canada), and in turn connected through physiological pressure transducers to a multi-channel polygraph recorder. First, the catheter was placed within the stomach (55 cm), and then slowly retracted by 0.5 to 1.0 cm increments to identify the lower esophageal sphincter (LES). With the tip of the catheter at the level of the respiratory inversion point (RIP), each patient did ten water swallows at least one minute apart. The total length and the intra-abdominal length of the LES, basal pressure, and resting pressure during relaxation, and the duration of LES relaxation were measured. All esophageal body wave amplitudes of 5 mmHg and over, during water swallows at the distal esophagus 5, 10, and 15 cm above the LES, were included in the analysis. Wave progression, peristalsis analysis, and propagation rates (cm/s) were assessed. The peristalsis was considered normal if 7 out of 10 water swallows were propulsive. The esophageal body was considered as low pressured if all the distal wave amplitudes were below 30 mmHg. In addition, the length (mm), the basal pressure (mmHg), and function of the upper esophageal sphincter (UES) were evaluated. The data were gathered onto a standardized data extraction sheet. The means of ten water swallows were calculated for each channel. Esophageal manometry data-capture and analysis were performed with the aid of a computer analysis program (Flexilog, Flexisoft III, Oakfield Instruments, Oxon, UK).

Esophageal histology

In addition to the traditional hematoxylin and eosin (HE) staining, the alcian blue periodic acid-Schiff (AB-PAS) double staining method (Voutilainen 1989) served to identify any goblet cells (Barrett´s esophagus). Biopsy specimens were fixed in 10% buffered formalin, embedded in paraffin, and stained with hematoxylin and eosin, as well as with alcian blue. Specimens were evaluated for the presence or absence of histological columnar epithelial metaplasia and esophagitis. Esophagitis was graded as none, mild, moderate, or severe according to Ismail-Beigi (1970). Samples with columnar epithelial metaplasia with no goblet cells (gastric metaplasia) or with goblet cells (intestinal metaplasia) were further evaluated with immuhistochemistry (IHC) for CDX2, an intestinal mucin-coding protein, and MUC2, a mucin marker (Silberg 2002, Eda 2003, Kerkhof 2006). These are both expressed in the normal intestine and in any intestinal metaplasia of the esophagus, but not in the normal esophagus. IHC stainings were performed in the LabVision immunostainer (Labvision, CA, USA). Antigen retrieval required Tris-EDTA buffer (pH 9.0) for the CDX2 antibody and citrate buffer (pH 6.0) for the MUC2 antibody in a microwave oven for 24 minutes at 900 watts, followed by cooling for 20 minutes at room temperature. The following primary antibodies were used: MUC2 (dilution 1:25 Novocastra, NCL-MUC2), and CDX2 (dilution 1:50, Biogenex, MU392A-UC). IHC studies utilized a polymer-based detection system (Envision, K5007, DakoCytomation), and the reaction was visualized with a diaminobenzidine (DAB) chromogen.

Respiratory morbidity (III)

Interview and questionnaire

Patients were interviewed on their respiratory and allergy symptoms and illnesses, and they filled out a modification of a standardized questionnaire on asthma and allergy symptoms (Pekkanen 1997), and on a respiratory symptom-related quality of life index (RSRQLI) (Juniper 1999). The cut-off point was set at < 44 of a possible 60 points for impaired respiratory symptom-related quality of life (Koivusalo 2005). Information provided was on medical history, respiratory symptoms and diseases, need for asthma medication, smoking habits, and symptoms of allergy. Respiratory symptoms included wheeze, attacks of shortness of breath, longstanding cough, respiratory infections, and asthma. Symptoms of allergy included allergic rhinitis, conjunctivitis, rash, atopic eczema, and allergic asthma.

Pulmonary function

All patients underwent flow volume spirometry for lung volumes, a histamine challenge test (HCT) for bronchial hyper-responsiviness (BHR), and an exhaled nitric oxide level (FE^{NO}) test for airway inflammation. Flow volume spirometry was performed according to guidelines of the European Respiratory Society (Quanjer 1993), and BHR was estimated by a dosimetric HCT (Sovijärvi 1993). The following parameters were recorded: forced vital capacity (FVC), forced expiratory volume during the first second (FEV1) (Figure 8), and their reference-value percentages. We used national reference values for spirometry published earlier (Viljanen). Ventilatory function was defined as restrictive when FVC was < 80%, which corresponds z-score -2.0, and obstructive when FEV1/FVC% was < 87% of predicted, which also corresponds to z-score -2.0. Defects were classified as mild (z-score -2.0 - -3.5), moderate (z-score -3.5 - -5.5), or severe (z-score -5.5 - -7.5). The dose-response curve allowed determination of the provocative dose of inhaled histamine producing a decrease of 15% in FEV1 (PD15FEV1). According to the PD15FEV1, BHR was graded as mild (0.41 - 1.60 mg), moderate (0.11-0.40 mg), or severe (≤ 0.1 mg) (Kharitonov 1997). Patients with PD15FEV1 ≤ 1.6 mg were considered hyperreactive. PD15FEV1 ≤ 0.4 mg was considered diagnostic for asthma and is here referred to as an asthma-like-response.

Fractional FE^{NO} was measured by computerized equipment with a chemiluminescence analyzer (Niox, Aerocrine AB, Sweden) according to ATS recommendations (1999). The patients were seated, without a nose clip, and were asked to fill their lungs completely with nitric oxide-free air, and thereafter to exhale with a steady and instantaneous flow of 50 + 5 ml/s. Exhalation time of 10 seconds served as the default. The system was calibrated with a certified nitric oxide calibration gas mixture according to manufacturer´s instructions. Exhalations that did not meet the ATS requirements were rejected by the system, and the patient was asked to perform new exhalation maneuvers until three acceptable end-expiratory plateau measurements could be calculated and recorded (Ekroos 2000, Taylor 2006). In the present study, the reference values for the distribution of FE^{NO} came from a study on adult lifelong non-smokers that used a similar technique; exhalation rate depending on age and height were used (Olin 2007).

Atopy

Atopy was defined as a positive reaction to a skin prick test (SPT) for common allergens. SPT was carried out for the following common allergens: birch, grass, mugwort, cat, dog, cow, horse, *Cladosporium herbarum*, and *Dermatophagoides pteronyssinus* (Soluprick SQ, ALK, Horsholm, Denmark). The patient was regarded as atopic if one or more reactions were positive, determined as a wheal diameter of 3 mm or greater in the presence of expected results with control solutions. The positive control solution was histamine dihydrochloride 10 mg/ml and the negative solution, saline. The urban adult population of Helsinki served as a comparison group for SPT (Pallasaho 2006). The level of serum immunoglobulin E (s-IgE) was based on the standard values of our laboratory, 0 to 110 kU/L for adults.

Musculoskeletal defects (IV)

Musculoskeletal symptoms

Patients were interviewed and completed a symptom questionnaire on musculoskeletal disturbances, neck or back pain, radiculopathy, and scoliosis.

Vertebral anomalies, spinal defects and scoliosis

The full orthopedic evaluation included range of motion of the neck and back, and measurement of rib and lumbar hump with a scoliometer in the forward bending test (Bunnell 1984), as well as range of motion of the spine with Schober's test with a skin contraction technique (Miller 1984), and measurement of the distance between the fingertips and floor. Leg-length discrepancy was evaluated with wooden blocks. A standing posteroanterior radiograph showed the thoracic and lumbar spine, and anteroposterior and lateral radiographs showed the cervical spine. Thoracic and lumbar curves and cervical kyphosis were measured with Cobb's technique (Cobb 1948). Incidence of scoliosis was compared with that of a general population in Finland (Nissinen 1993).

Other skeletal anomalies and defects

The clinical assessment allowed examination of the trunk and extremities. Shoulder asymmetry was measured with a ruler for height difference between the shoulders. Waist asymmetry and trunk asymmetry were assessed subjectively (yes/no). The lower extremities were assessed for any length discrepancy with wooden blocks, and for radiculopathy with the straight-leg raising test (Lasegué test 1967, Devillé 2000). Upper extremities were evaluated for range of motion (function of the nervus thoracicus longus), and for radial ray anomalies. Suspicion of hand anomalies required radiographs of the hands.

STATISTICAL ANALYSIS

Cancer (I)

Follow-up for cancer was performed automatically, based on personal identification codes, in a linkage with the population-based countrywide Finnish Cancer Registry. The Finnish Cancer Registry maintains records of all cancer patients from every medical facility in Finland. The number of cancer cases observed and the number of person-years at risk was counted, and the expected number of cancer cases was calculated by multiplying the number of person-years by the corresponding cancer incidence in all of Finland. To calculate the standardized incidence ratio (SIR), the number of cancer cases observed was divided by the expected. Exact 95% confidence intervals (CIs) were defined on the assumption that the number of cases observed followed a Poisson distribution.

Clinical long-term outcomes (II-IV)

Data analysis (II-IV) was with SPSS 16.0 (SPSS Inc., Chicago, IL, USA). The chi-square (χ^2) test served to compare frequences (II-IV). Continous variables were compared with the Kruscal-Wallis test (II, III, IV) with a subsequent Dunn´s test (II). Multivariate logistic regression was used to evaluate independent risk factors for epithelial metaplasia (II), restrictive ventilation defect (III), vertebral anomalies (IV), and scoliosis (IV). Odds ratios (OR) and their 95% confidential intervals (CI) are given. Level of statistical significance was set at 0.05.

Results

OUTCOMES

Patients and controls

A total of 169 (72%) patients and 287 (31%) controls replied, and a cohort of 101 (43%) patients representative of the entire study population participated in the clinical assessments. Of the 101 patients, 58 were male, and mean age at the clinical evaluation was 36 (range, 21-57) years. As shown in Table 6, the participants and non-participants were comparable in terms of age, gender, type of EA, associated anomalies, and surgical complications (P=ns).

Table 7. *Characteristics of study participants and non-participants*

	Participants N (%)	Non-participants N (%)
Number	101 (100)	161 (100)
Male gender (%)	58 (58)	83 (64)
Age in years, mean (range)	36 (21 – 57)	37 (21 – 57)
Body mass index, mean (range) (kg/m^2)	24 (21 – 45)	-
Esophageal atresia (%)		
with proximal TEF	2 (2)	3 (2)
with distal TEF	91 (91)	120 (89)
with double TEF	5 (5)	10 (7)
Only TEF	3 (3)	3 (2)
Associated anomalies primarily (%)	30 (30)	56 (35)
Associated anomalies currently (%)	72 (72)	-
VACTERL primarily (%)	5 (5)	8 (5)
VACTERL currently (%)	23 (23)	-
Anastomotic complications (%)		
Leak	4 (4)	4 (3)
Recurrent TEF	10 (10)	10 (7)
Stricture requiring resection	4 (4)	3 (2)
Antireflux surgery (%)	10 (10)	8 (6)

TEF, tracheoesophageal fistula

VACTERL, vertebral defects – anal atresia – cardiaovascular anomalies –tracheoesophageal fistula with esophageal atresia – radial and renal dysplasia – limb defects

Cancer (I)

All patients treated for EA in our hospital between 1949 and 1978 were screened for cancer. None of the 502 patients was lost to follow-up. A total of 230 patients who died before 1967 under the median age of 8 days were excluded from further analysis. The 272 remaining patients (142 males) were eligible for follow-up at a median age of 35 years (range, 2 days to 56 years). The number of person-years at risk was 8034 (Table 8). Of the three cases of cancer found (SIR, 1.0; 95% CI, 0.20-2.8) (Table 9), one was lymphoma in the small intestine, one leukemia, and one carcinoma of the uterus; none was esophageal cancer. The overall cancer incidence among our EA patients did not differ from that of the general Finnish population. Our study showed that the statistical risk for esophageal cancer after repair of EA is less than 500-fold that of the general population.

Table 8. *Person-years at risk among Finnish patients with EA in 1967-2004 by age and sex*

Age (years)	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

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Table 9. *Observed and expected numbers of all cancer cases and standardized incidence ratios (SIRs) with their 95% confidence intervals (CIs) among Finnish patients with EA in 1967-2004*

Age (years)	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

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Esophageal morbidity (II)

Typical esophageal symptoms included regurgitation, heartburn, dysphagia, esophageal food bolus obstruction, and aspiration. Necessary dietary modifications included avoidance of certain foods, and abundant liquied intake with food (Table 10). Symptomatic GER occurred in 34%, and dysphagia in 85% of the patients, and in 8% and 2% of the controls (P<0.001 for both).

Table 10. *Prevalence of gastroesophageal reflux (GER) symptoms and dysphagia in adult patients with repaired esophageal atresia according to esophageal histology*

	All N=101	Normal N=61	Esophagitis N=19	Metaplasia N=21	P (χ^2–test)
GER	34 (34)	20 (33)	6 (32)	8 (38)	0.89
Antireflux medication	10 (10)	5 (8)	3 (16)	2 (10)	0.65
Antireflux surgery	10 (10)	4 (7)	2 (10)	4 (19)	0.29
Dysphagia	85 (85)	49 (80)	17 (89)	19 (91)	0.41
Abundant food drink	79 (79)	45 (74)	15 (79)	19 (91)	0.23
Careful chewing	56 (56)	31 (51)	12 (63)	13 (62)	0.51
Both drinking and chewing	50 (50)	27 (44)	10 (53)	13 (62)	0.36
Foreign body removal	32 (32)	16 (26)	9 (47)	7 (33)	0.23

Endoscopic findings included hiatal hernia (28%), Barrett´s esophagus (11%), esophagitis (8%), and anastomotic stricture (8%). Three patients had an esophageal diverticulum at the site of the anastomosis, and one recurrent TEF was found and treated successfully by bronchoscopy and laser. The LA grade of the esophagitis was LA-A in four, LA-B in two, LA-C in one, and LA-D in one.

Histology and IHC revealed esophagitis in 25% and CDX2-positive columnar epithelial metaplasia in 21%, with additional goblet cells and MUC2-positivity in 6% (Table 11). Nuclear CDX2 positivity appeared in 47% of the cases of columnar metaplasia without goblet cells. All samples with moderate esophagitis were associated with epithelial metaplasia. Gastric metaplasia and intestinal metaplasia are demonstrated in HE, AB-PAS, and CDX2 stainings, and intestinal metaplasia also in MUC2 staining (Figures 8 and 9). None of the patients had esophageal dysplasia or carcinoma. GER and dysphagia were equally common in individuals with normal histology, esophagitis, or epithelial metaplasia. Nuclear staining for CDX2 was often confined to the surface epithelium, whereas the focal cytoplasmic staining for CDX2 was located in the deeper portion of the glands.

Table 11. *Esophageal histology and immunohistochemistry in 101 adults with repaires esophageal atresia*

	N=101	Cytoplasmic CDX2	Nucleic CDX2	MUC2
Esophagitis	25	-	-	-
Columnar metaplasia without goblet cells	15	12/15	7/15	0/15
Columnar metaplasia with goblet cells	6	6/6	6/6	6/6
Any abnormality	39	-	-	-

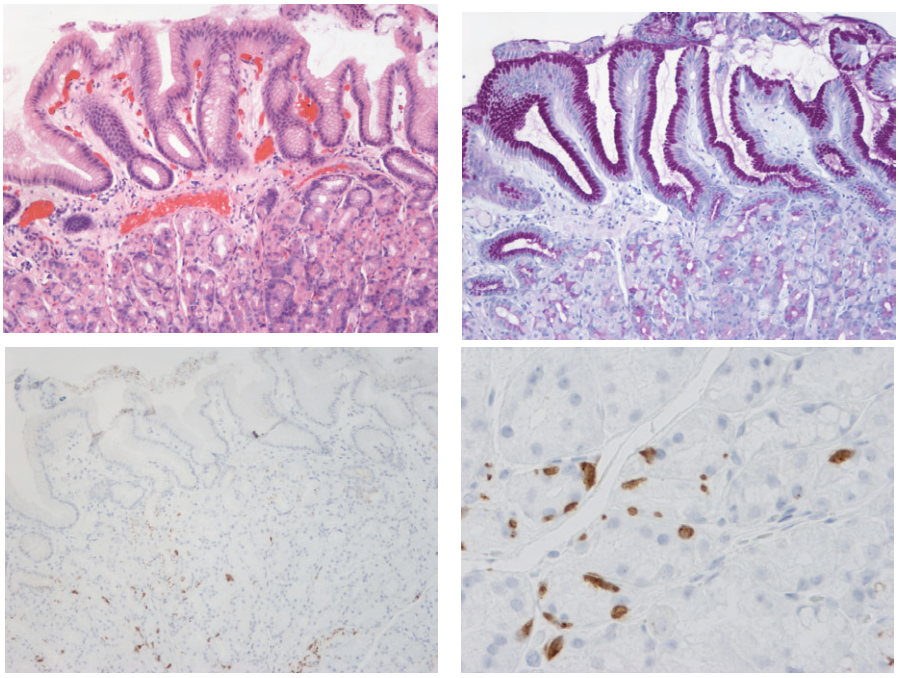

Figure 8 *A 41-year-old male with columnar metaplasia without goblet cells of the distal esophagus in HE (A), AB-PAS (B), and CDX2 (C-D) stainings in 100-fold (2A-C) and 400-fold (2D) enlargement*

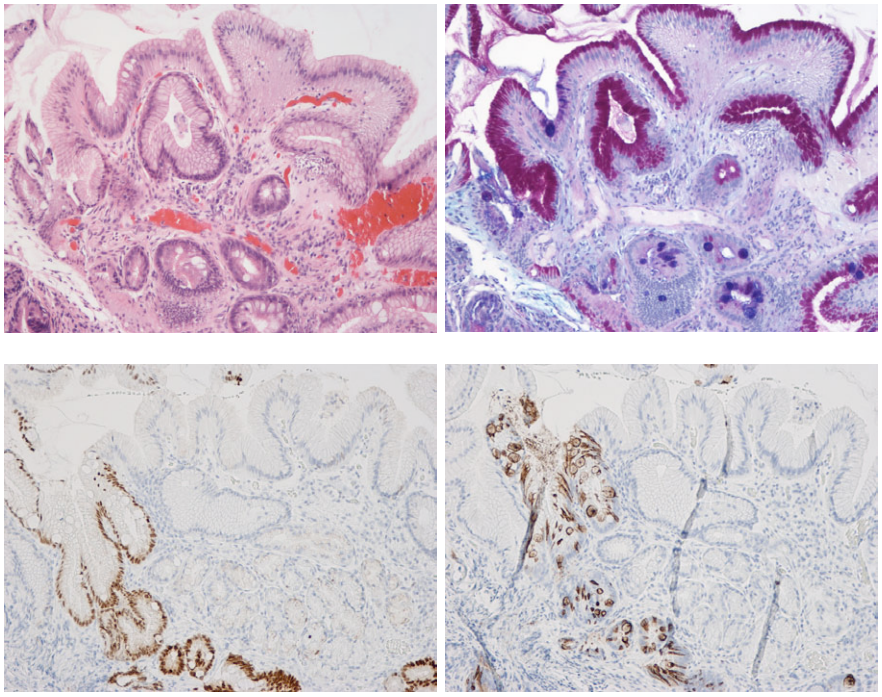

Figure 9 *A 22-year-old male with columnar metaplasia with goblet cells of the distal esophagus in HE (A), AB-PAS (B), CDX2 (C), and MUC2 (D) stainings in 100-fold enlargements*

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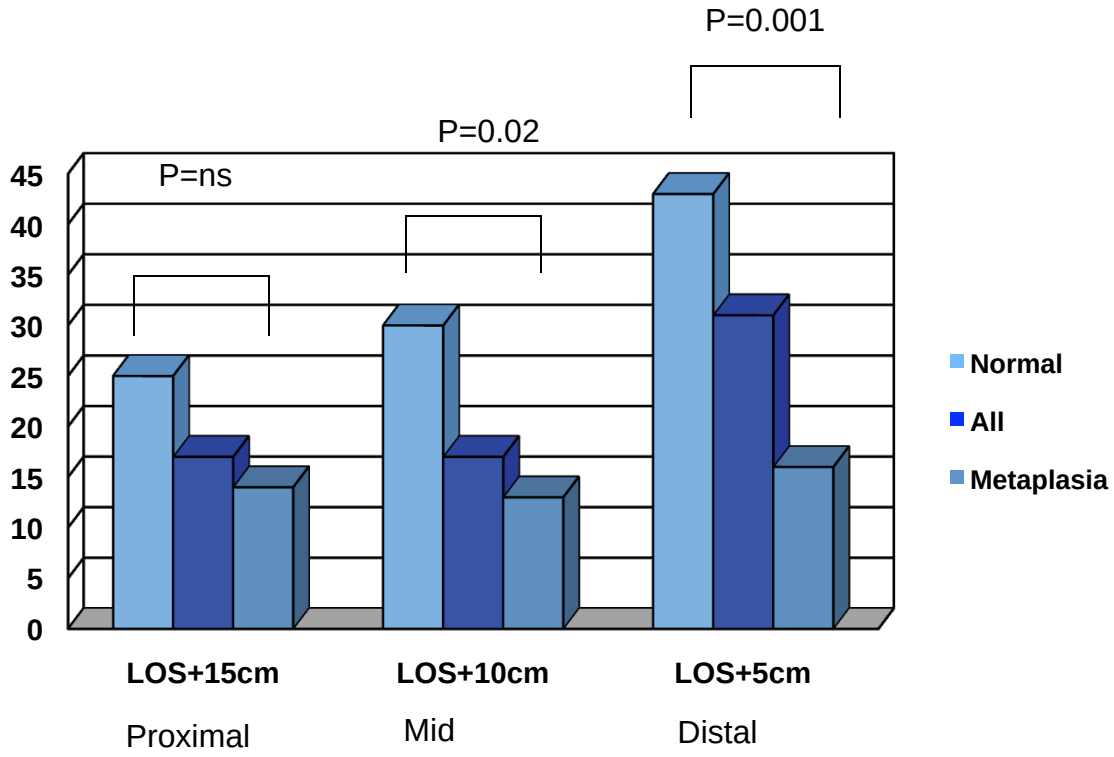


Figure 10 *Esophageal distal wave amplitudes in the proximal, mid, and distal esophagus*

Bars represent wave amplitudes of the esophagus. The first column represents the minimum of normal values, the second, a median value for all patients, and the third, the value for patients with metaplasia. Normally, distal wave amplitudes grow stronger when moving from the proximal esophagus to the distal esophagus. All adult patients with repaired EA have low distal wave amplitudes, and patients with metaplasia even lower, with the difference between all the patients and patients with metaplasia significant in the mid and distal esophagus. In addition, none of the patients with epithelial metaplasia exhibited propagating peristalsis, and the difference between all patients and patients with metaplasia was significant (P=0.001-0.02).

Esophageal manometry demonstrated non-propagating peristalsis in 80% of the patients, and low ineffective distal wave amplitudes of the esophagus in all (Table 12). The changes were significantly worse in those with epithelial metaplasia (P≤0.022 metaplasia versus esophagitis/normal) (Figure 10).

Table 12. *Results of esophageal manometry in adult patients with repaired esophageal atresia according to esophageal histology*

	All (N=101)	*Normal (N=61)*	*Esophagitis (N=19)*	*Metaplasia (N=21)*	*P**
UES, Median (IQR)					
Length (mm)	30 (30 – 40)	30 (30 – 40)	30 (20 – 35)	38 (30 – 40)	0.13
Basal pressure (mmHg)	43 (34 – 50)	40 (34 – 50)	50 (43 – 70)	40 (29 – 50)	0.14
ESOPHAGEAL BODY					
Distal wave amplitudes, Median (IQR)					
LES + 15 cm (mmHg)	17 (12 – 23)	18 (14 – 25)	18 (14 – 25)	14 (12 – 18)	0.15
LES + 10 cm (mmHg)	17 (13 – 25)	18 (14 – 27)	20 (14 – 31)	13 (12 – 18)[1]	0.02
LES + 5 cm (mmHg)	31 (17 -44)	33 (22 – 45)	37 (21 – 52)	16 (13 – 25)[2]	0.001
Low pressured N (%)	82 (82)	49 (80)	20 (95)	20 (95)[3]	0.028
Wave peaks, N (%)					0.020[4]
Single	12 (12)	10 (16)	1 (5)	1 (5)	
Double	58 (58)	35 (57)	14 (74)	9 (43)	
Multi	12 (12)	6 (10)	2 (11)	4 (19)	
Repeated	15 (15)	7 (12)	1 (5)	7 (33)	
Peristalsis analysis, N (%)					0.011[5]
Propagating	20 (20)	14 (23)	6 (32)	0 (0)[6]	
Non-propagating	80 (80)	46 (77)	13 (68)	21 (100)[6]	
Incomplete sequences	73 (73)	43 (74)	13 (68)	17 (81)	
Retrograde sequences	49 (49)	27 (49)	6 (32)	16 (76)	
Propagation rate (cm/s)	2.6 (2.2-2.9)	2.6 (1.8-3.6)	2.5 (2.2-2.9)	0 (0)	
LES, Median (IQR)					
Intra-abdominal length (mm)	15 (10 -20)	20 (10 – 20)	15 (10 – 20)	0.64	
Total length (mm)	40 (30 – 40)	40 (30 – 40)	40 (30 – 40)	0.72	
Basal pressure (mmHg)	20 (15 -25)	21 (18 – 30)	16 (14 – 25)	0.21	

* Kruscal-Wallis test and subsequent Dunn´s test were used to compare continuous variables, and χ^2 –test to compare frequences between different histological subgroups

[1]Epithelial metaplasia vs. esophagitis P=0.036, epithelial metaplasia vs. normal P=0.039

[2]Epithelial metaplasia vs. esophagitis P=0.003, epithelial metaplasia vs. normal P=0.001

[3]Epithelial metaplasia vs. esophagitis P=0.018

[4]Progressive wave peak derangement in linear-by-linear analysis within different histological subgroups.

[5]Significant shift towards non-propagating peristalsis in linear-by-linear analysis within different histological subgroups

[6]Epithelial metaplasia vs. esophagitis P=0.006, epithelial metaplasia vs. normal P=0.022.

Patients with esophageal columnar metaplasia have had more anastomotic complications than do the rest of the patients. The incidence of early stricture resection, recurrent TEF, long gap requiring myotomy, and late stricture was higher among patients with columnar metaplasia (Table 13).

Table 13. *Anastomotic complications*

Complication	All (n=101) N (%)	Metaplasia (n=21) N (%)	P-value
Early stricture resection	4 (4)	3 (14)	0.06
Recurrent fistula	10 (10)	6 (29)	0.02
Late stricture	8 (8)	5 (24)	0.03
Long gap requiring myotomy	5 (5)	4 (19)	0.03

Predictors of esophageal metaplasia

Anastomotic complications (OR 8.6-24, 95%CI 1.7-260, P=0.011-0.008), increasing age (OR 20, 95%CI 1.3-310, P=0.034), low esophageal distal wave amplitudes (OR 2.6, 95%CI 0.7-10, P=0.002), and defective esophageal peristalsis (OR 2.2, 95%CI 0.4-11, P=0.014) predicted development of epithelial metaplasia (Table 14). Of the patients with epithelial metaplasia, 72% were male, and 76% were older than 30. Occurrence of epithelial metaplasia was associated with increasing age (Figure 11).

Table 14. *Multivariate logistic regression model for occurrence of esophageal epithelial metaplasia*

	OR (95%CI)	P-value
Early stricture resection	24.0 (2.3 – 260)	0.008
Recurrent fistula	24.0 (2.2 – 250)	0.009
Age >30 y	20.0 (1.3 – 310)	0.034
Long gap requiring myotomy	19.0 (2.0 – 180)	0.011
Late stricture	8.6 (1.7 – 45)	0.011
Distal wave amplitudes <25 mmHg	2.6 (0.68 – 10)	0.002
Non-propagating peristalsis	2.2 (0.43 – 11)	0.014

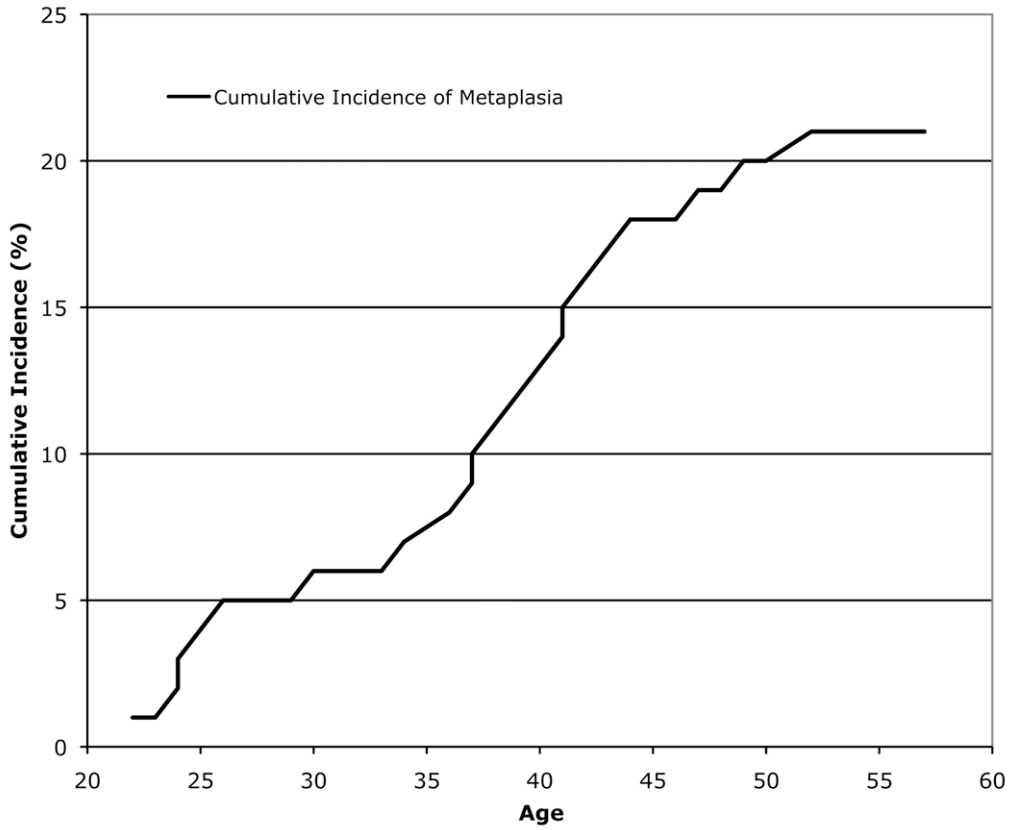


Figure 11 *Association between increasing age and occurrence of epithelial metaplasia*

Respiratory morbidity (III)

Participants and non-particiants were similar in relation to primary tracheo-pulmonary morbidity (Table 15). Of the patients, 34% had pneumonia as a primary pulmonary complication, 33% not had no postoperative ventilation, and the mean postoperative ventilation time was 2.6 days (range, 0-7). During childhood, tracheomalacia was diagnosed in 15%, but only 1% had undergone aortopexy. A total of 10% patients had recurrent TEF.

Table 15. *Tracheo-pulmonary morbidity at the time of the primary repair of esophageal atresia among participants and non-participants*

	Participants (N=101) N (%)	Non-participants (N=161) N (%)
Primary pneumonia	34 (34)	47 (33)
Need for postoperative ventilation		
None	33 (33)	66 (41)
For 1 day	6 (6)	25 (16)
2 days	22 (22)	27 (17)
3 – 6 days	26 (26)	31 (19)
Over 7 days	13 (13)	15 (9)
Tracheostomy	1 (1)	0
Tracheomalacia	15 (15)	13 (8)
Aortopexy	1 (1)	4 (2)
Recurrent TEF	10 (10)	10 (7)

No significant differences between participants and non-participants (χ^2-test: p>0.076)

Respiratory symptoms

Recurrent respiratory infections in childhood occurred in 35% of the patients and in adulthood in 52%. Factors predisposing to respiratory symptoms and infections in adulthood were GER and recurrent TEF with recurrent aspiration. In the present series, three patients had developed irreversible lung damage with bronchiectasis and chronic respiratory infections. The patients had significantly more respiratory symptoms and infections as well as asthma, allergy, and impaired respiratory symptom-related quality of life when compared with those of controls (Table 16).

Pulmonary function

Results of pulmonary function, bronchial responsiveness, and airway inflammation are presented in Table 17. Only 20% of the patients had normal PF. Over half the patients had restrictive, obstructive, or both of these ventilatory defects. Of the patients, 41% had BHR, and FE^{NO} was elevated in eleven patients indicating airway inflammation.

Table 16. *Self-reported incidence of asthma, allergy, and respiratory symptoms of the participants with repaired esophageal atresia (n=101) and of the controls (n=287)*

	Patients (%)	Controls (%)	P-value
Impaired RSRQLI*	11	6	0.001
Current respiratory symptoms	11	2	0.001
Doctor-diagnosed asthma	16	6	0.001
Wheeze	37	30	NS
Allergy	42	11	0.002
Persistent cough	31	8	0.001
Pneumonia	56	20	0.001
Bronchitis	70	50	0.001
Recurrent infections	52	23	0.001
Childhood infections	35	13	0.001

*RSRQLI – Respiratory symptom-related quality of life index (Juniper 1999), NS – not significant

Table 17. *Pulmonary function, bronchial hyperresponsiveness, exhaled nitric oxide, and skin prick test among adults with repaired esophageal atresia (n=101)*

Variable	Result Mean (range)	Abnormal (%)	Grade Mild	Moderate	Severe
Age (years)	36 (21 – 57)				
Body mass index (kg/m^2)	24 (21 – 45)				
Spirometry					
FVC % of predicted	77 (53 – 120)	57%	28%	28%	1%
FEV1 % of FVC predicted	100 (72 – 119)	57%	25%	29%	3%
Restriction (FVC < 80%)		21%	18%	3%	0
Obstruction (FEV1/FVC < 87%)		21%	15%	4%	2%
Both restriction and obstruction		36%	10%	25%	1%
Histamine challenge test					
PD15FEV1 (mg)	0.65 (0.03 – 1.60)	41%	26%	11%	4%
PD15FEV < 0.4mg		15%	-	-	-
Exhaled nitric oxide elevated		11%	7%	4%	0
Skin prick test positive		37%	15%	-	22%

FVC – forced vital capacity, FEV1 – forced exhaled volume in one second, PD15FEV1 – provocative dose of histamine causing a 15% fall in FEV1

Restriction = FVC < 80% = Z-score < -2.0, obstruction = FEV1/FVC < 87% = Z-score < -2.0

Atopy

In SPT for common allergens, a total of 37% had at least one positive reaction. Sensitization to multiple allergens was evident in 22%. The most common allergens were dog (28%), cat (22%), birch (23%), mugwort (22%), and timothy (21%). A total of 12% had a positive reaction to *Dermatophagoides pteronyssinus*, and 8% to *Cladosporium herbarum*. Serum immunoglobulin E level was elevated (>110 kU/L) in 20% (median 285 kU/L, range 126-2436).

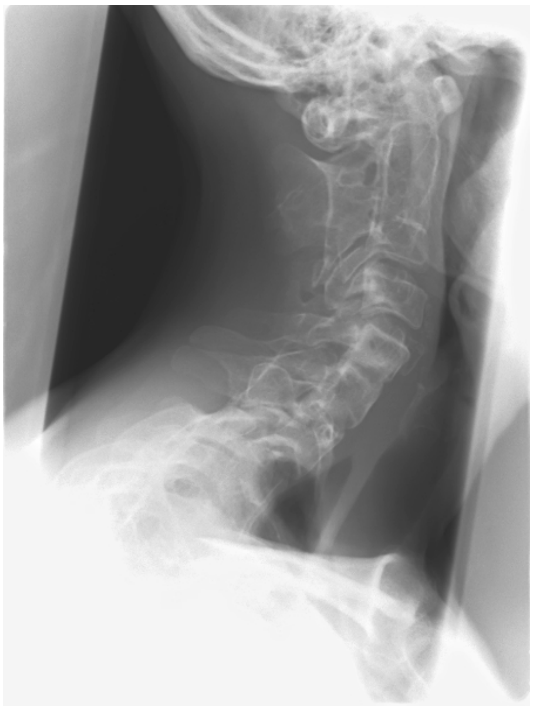
Predictors of restrictive ventilation defect

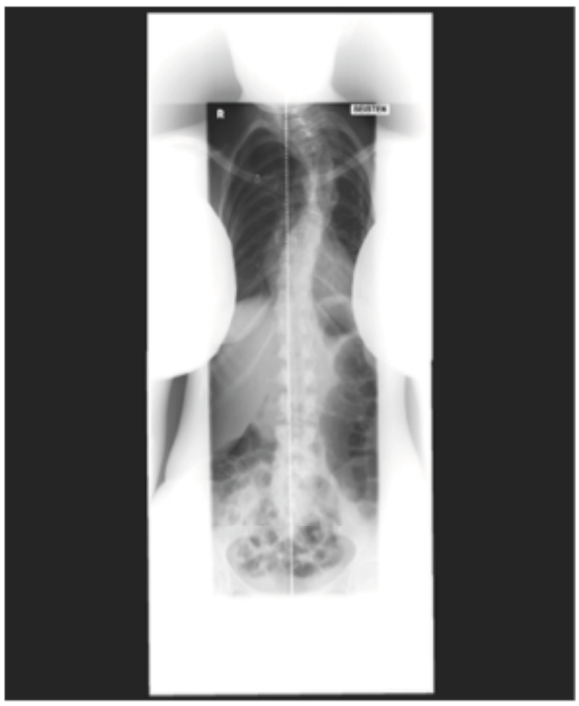
Adults with repaired EA had significantly more respiratory problems than did controls (P≤0.002). Thoracotomy-induced rib fusions (OR 3.4, 95%CI 1.3-8.7, P=0.01), and surgical complications leading to GER-associated esophageal epithelial metaplasia (OR 3.0, 95%CI 1.0-8.9, P=0.05) predicted restrictive ventilatory defect that occurred in 57% of the adults with repaired EA.

Musculoskeletal defects (IV)

Full orthopedic evaluation included radiographs of the spine. Waist asymmetry was rare. Shoulder asymmetry (mean 14 mm, range 10-40 mm) was evident in 80% of the patients, and chest asymmetry in 15%. Over half (54%) of the patients had a rib or lumbar hump over six degrees, indicating clinically scoliosis. Length discrepancy of the lower extremities (mean 13 mm, range 6-20 mm) occurred in 13%, and none of the patients had radiculopathy. A total of 20% had a limited range of motion of the right upper extremity. Radial ray anomalies were evident in 25%, of which most were thenar aplasias or hypoplasias. No difference appeared in musculoskeletal symptoms between the patients and controls (P=ns).

In radiographs of the spine, vertebral anomalies were evident in 45% of the patients, predominating in the cervical spine in 38%. Most of these were cervical vertebral fusions (Figure 12) in C2-3 and C6-7. Any associated anomaly was the most significant risk factor (OR 27, 95%CI 8-100) for the occurrence of vertebral anomalies (Table 18). Scoliosis over 10 degrees was observable in 56% of the patients, over 20 degrees in 11%, and over 45 degrees in 1% (Figure 13). The risk for scoliosis over 10 degrees was 13-fold (OR 13, 95%CI 8.3-21), and for scoliosis over 20 degrees 38-fold (OR 38, 95%CI 14-106) that for the normal population (Table 19). Thoracotomy-induced rib fusions (OR 3.6, 95%CI 0.7-19) and other associated anomalies (OR 2.1, 95%CI 0.9-2.9) were the strongest predictive factors for scoliosis (Table 20). The general clinical course of spinal deformities was mild, and none of the patients had undergone spinal surgery.





Figures 12 and 13 *Radiograph of cervical spine with multiple vertebral fusions and of severe thoracic scoliosis*

Table 18. *Risk for scoliosis in patients compared to controls from study of Nissinen (1993)*

Degrees of scoliosis	Patient group (N=100) N (%)	Control population (N=855) N (%)	OR (95%CI)	P-value
> 10°	56 (56)	79 (9.2)	13.2 (8.2 – 21.0)	<0.001
> 20°	11 (11)	6 (2.4)	37.8 (13.5 – 106)	
> 45°	1 (1)	0		

OR – odds ratio

Table 19. *Univariate logistic regression model of risk factors for vertebral anomalies*

Variable	OR (95%CI)	P-value
Gender	1.3 (0.6-2.9)	0.49
Any additional anomaly	27.4 (7.5-100)	< 0.001
VACTERL	7.3 (2.5-22.9)	<0 .001
Anorectal malformation	1.4 (0.3-7.2)	0.71
Cardiac anomaly	2.9 (0.5-16.5)	0.24
Other gastrointestinal	1.6 (0.4-6.4)	0.49
Renal anomaly	0.6 (0.1-3.8)	0.62
Limb anomaly	4.5 (1.5-13.4)	0.008

OR – odds ratio, VACTERL – vertebral anomalies, anorectal malformations, cardiac defects, tracheoesophageal atresia, renal anomalies, and limb defects

Table 20. *Univariate logistic regression model of risk factors for scoliosis*

Variable	OR (95%CI)	P-value
Gender	1.2 (0.6-2.9)	0.60
Previous heart surgery	2.0 (0.4-10.9)	0.40
Rib fusions	3.6 (0.7-19.4)	0.13
Any additional anomaly	2.1 (0.9-4.8)	0.07
VACTERL	1.3 (0.5-3.4)	0.59
Vertebral anomaly	1.5 (0.8-2.8)	0.23
Anorectal malformation	1.6 (0.3-9.3)	0.59
Cardiac anomaly	2.0 (0.4-10.9)	0.40
Other gastrointestinal	3.9 (0.5-30.4)	0.19
Renal anomaly	1.0 (0.4-2.6)	0.94
Limb anomaly	1.6 (0.6-4.5)	0.35

OR – odds ratio, VACTERL – vertebral anomalies, anorectal malformations, cardiac defects, tracheoesophageal atresia, renal anomalies, limb defects

Discussion

METHODOLOGY

To the best of our knowledge, this was the first population-based long-term follow-up study among adults with repaired EA. The first 101 patients who replied were included to the clinical studies. We were able to identify 100% of them and trace 90% of the entire study population.

The first study (I) was a cross-sectional register study on cancer following EA repair. Comparison of data from a patient record review, the Finnish Population Register Center, and the Finnish Cancer Registry enabled us to study the incidence of cancer among individuals with repaired EA compared to that of the general population. The patient sample was all-inclusive, because none of the 502 patients was lost to follow-up. The Finnish Cancer Registry is population-based, covering the whole of Finland and having multiple independent sources of notification of cancer, which ensures the completeness of the registry and accuracy of its data. The cancer registration system is virtually all-inclusive (Teppo 1994), and the computerized record linkage procedure by the Cancer Registry is precise (Pukkala 1992). Technical failures in linkages or incompleteness in the follow-up are therefore very unlikely.

The three other studies (II-IV) were cross-sectional follow-up studies. We limited the sample size to 101 patients. Patients were included in the order they replied to the invitation, meaning that asymptomatic individuals were also included. Despite the burdensome study protocol including invasive investigations, the overall response rate was high (72%), and we performed a drop-out analysis in order to assess possible selection bias between participants and non-participants. These participants and non-participants were similar in terms of gender distribution, age, distribution of type of esophageal atresia, frequency of associated anomalies, surgical complications, and frequency of antireflux surgery, making any significant selection bias among the patients very unlikely.

Concerning esophageal (II) and respiratory (III) symptoms, we used validated symptom questionnaires to add in comparability. Identical questionnaires were also mailed to individuals with repaired EA not attending the clinical studies and to general population-derived controls matched for age, sex, and municipality of residence (II-IV). The study protocol for the prospective clinical studies was carefully planned, and the results were evaluated in collaboration with experts from different fields. Our methods were recommended standard procedures that are widely accepted. All patients, including those with no apparent symptoms, underwent the same studies. Statistical methods were appropriate.

In the study concerning esophageal morbidity (II), endoscopic esophagitis was graded according to the Los Angeles classification (Armstrong 1996) and histological esophagitis according to Ismail-Beigi (1970). Both methods are widely accepted. Columnar epithelial metaplasia was further evaluated with IHC to demonstrate early Barrett (gastric metaplasia) and change to Barrett (intestinal metaplasia). In esophageal manometry analysis, all low esophageal body pressures were checked manually.

In the third study, on respiratory morbidity (III), we also used validated questionnaires with controls derived from the general population that were matched for age, gender, and municipality of residency. A drop-out analysis between participants and non-participants suggested that the two groups were comparable with respect to primary disease characteristics, minimizing risk for selection bias. We used standard methods for evaluating PF (flow volume spirometry, HCT, and FE^{NO}) and sensitivity to common allergens (SPTs), and so comparison with other population-based results from Finland seem justified.

In the fourth study we assessed the natural history of spinal anomalies and scoliosis (IV). Evaluation of scoliosis was performed according to Bunnell´s criteria (1984) in the clinical assessment, and according to Cobb´s technique (1948) in the radiographs, both of which are acknowledged methods for screening scoliosis. Vertebral and other skeletal anomalies were sought systematically in clinical assessment and screened from radiographs of the spine.

CANCER

Our major finding was the absence of any cases of esophageal cancer among our EA patients. The crude incidence of esophageal cancer in 2003 in Finland was 4.3/100 000, with approximately 220 new cases annually (Finnish Cancer Registry). Our study was able to exclude long-term risk for esophageal cancer after repair of EA any higher than 500-fold that of the general population. The overall cancer incidence among the EA patients did not differ from that of the general Finnish population.

This study is, to our knowledge, the first epidemiological assessment of the occurrence of esophageal cancer among patients with repaired EA. Our study cohort of 502 patients included every EA patient operated on at one hospital between 1949 and 1978, and the follow-up was complete until 2004. We are aware of no earlier series of a consecutive patient population followed up for almost 60 years.

To date, six case reports of esophageal cancer among adults with repaired EA have appeared worldwide. LaQuaglia (1987) reported a 45-year-old female, Deurloo (2001) a 38-year-old male, and Taylor (2007) a 44-year-old female, each of whom had repaired EA and had developed a squamous cell carcinoma of the esophagus. Aznick (1989), Pultrum (2005), and Alfaro (2005), each reported a young female patient with esophageal adenocarcinoma. The patients were 20, 22, and 46 years of age at the time of diagnosis. Thus, esophageal cancer was diagnosed at an exceptionally early age in all, and none had any other apparent risk factors for esophageal cancer such as smoking, excessive alcohol consumption or malnutrition.

We studied an old cohort of survivors of EA in Finland, including the very first survivor. Although the oldest living EA patients are now reaching their sixties, the majority are below 40. However, the EA patients reported as having esophageal cancer have all been relatively young and clearly within the age range of our study cohort. The real cancer risk becomes evident when the majority of the patients with repaired EA will survive and grow older.

We specifically included gastric cancer in the analysis to allow us to include cancer of the cardiac region of the stomach that may be difficult to differentiate from cancer of the distal esophagus. There were no cases. As well as GER, after repair of EA, respiratory complications frequently occur

and may persist lifelong. Adults with repaired EA have been reported as having chronic bronchitis, recurrent aspiration of gastric contents, asthma, recurrent pneumonia, obstructive and restrictive ventilatory defects, airway hyperreactivity, and chronic pulmonary disease (Engum 1995, Chetcuti 1988 and 1993, Kovesi 2004). Chronic inflammation of the airways may potentially give rise to epithelial alterations and even cancer. However, we found no lung or laryngeal cancer cases among Finnish EA patients.

ESOPHAGEAL MORBIDITY

We analyzed, apparently for the first time in a population-based manner, esophageal morbidity in adults with repaired EA. Symptomatic GER occurred in 34% and dysphagia in 85% of the patients, while 25% demonstrated histological esophagitis and 21% CDX2-positive columnar epithelial metaplasia of the esophagus. Surgical complications, impaired esophageal motility, and age of the patients were significant predictors of development of epithelial metaplasia, suggesting that a primary esophageal anastomosis under tension and re-operations due to surgical complications further impair esophageal motility, predisposing to epithelial metaplasia with increasing age.

Based on relatively strict criteria for GER, 34% of the patients were classified as symptomatic; the figure was markedly less, 8%, among controls. GER symptoms and medically or surgically treated GER were equally common in patients with normal esophageal histology, esophagitis, or epithelial metaplasia. Prevalence of GER symptoms among adult EA patients has ranged between 17% and 75% (Orringer 1977, Chetcuti 1992, Krug 1999, Tovar 1995, Tomaselli 2002, Deurloo 2003 and 2008, Taylor 2007). The higher incidence of GER in most of these studies may result mainly from differing criteria and definitions of symptoms. It may also be difficult to reliably differentiate dysphagia-derived symptoms from those caused by GER. We had strict criteria for GER, and the occurrence rate of 34% was in accordance with others´ results. The present study represents, however, the first adequately controlled population-based series on this subject.

The reported incidence of dysphagia ranges between 48% and 72% (Orringer 1977, Chetcuti 1992, Tovar 1995, Tomaselli 2002, Konkin 2003, Little 2003, Taylor 2007, Deurloo 2008). The difference between incidences depends mostly on the definition of dysphagia. Our adding to symptoms of dysphagia included need for dietary modification, careful chewing, and abundant liquid intake during eating to ease swallowing difficulties, which may explain our high occurrence of dysphagia (85%). Most patients have had symptoms of dysphagia all their lives and do not recognize them as symptoms, considering them merely normal.

Late complications such as esophageal stricture have been reported in 30 to 56% and recurrent TEF in 5 to 14% (Engum 1995, Konkin 2003, Kovesi 2004, Spitz 2007, Lilja 2008). Our criterion for anastomotic stricture was obvious anastomotic narrowing in esophageal endoscopy. That, along with our study sample including patients both with and without symptoms, explains our lower occurrence of anastomotic stenosis (8%). A total of 10% with history of recurrent fistula was in line with previous results.

In this study, the prevalence of histological esophagitis was 25%, a figure lower than the prevalences between 33% and 90% reported among adults with repaired EA (Biller 1987, Krug 1999, Deurloo 2003, Tomaselli 2003, Deurloo 2005, Taylor 2007). Our study represents the largest cohort of adult EA patients with the longest follow-up, extending to 57 years and including the very first survivor in Finland. In total, only 58% of the selected participants in the studies listed underwent

endoscopy and histological examination of the esophagus, possibly contributing to their higher detection rate of esophagitis.

Columnar epithelial metaplasia in the esophagus is a pre-neoplastic condition arising as a result of GER. However, it is still unclear whether the presence of intestinal metaplasia is required for neoplastic potential (Lambert 2007). Six cases of esophageal cancer among young adults with repaired EA have been reported worldwide (LaQuaglia 1987, Adzick 1989, Deurloo 2001, Alfaro 2005, Pultrum 2005, Taylor 2007). In our study, IHC revealed CDX2-positive columnar epithelial metaplasia in 21%, with additional goblet cells and MUC2 positivity (intestinal metaplasia) in 6%. All cases of intestinal metaplasia were positive for nucleic and cytoplasmic CDX2 and cytoplasmic MUC2. In addition, nuclear CDX2 positivity occurred in 47% of the cases of columnar metaplasia without goblet cells. In the absence of goblet cells, CDX2 expression appears to predict the presence of undetected intestinal metaplasia that will become evident in follow-up biopsies later (Quinlan 2007). Among adults with repaired EA, frequency of intestinal metaplasia has ranged between 0% and 12% (Biller 1987, Tovar 1995, Krug 1999, Deurloo 2003, Taylor 2007). Based on these findings, the prevalence of Barrett´s esophagus seems at least four-fold higher among an adult population with repaired EA than among the general population (Ronkainen 2005). In addition, in the present study the incidence of histological esophagitis and histologically confirmed Barrett´s esophagus are in accordance with reported levels (Biller 1987, Krug 1999, Deurloo 2003, Deurloo 2005, Taylor 2007).

EA is associated with esophageal dysmotility with low distal wave amplitudes and non-propagating peristalsis of the esophagus (Orringer 1977, Tovar 1995, Tomaselli 2003, Kawahara 2007). Our results showed that the great majority (80%) had non-propagating peristalsis and all had low ineffective distal wave amplitudes of the esophageal body. Lengths and pressures of both esophageal sphincters were comparable to normal values (Mittal 2004, Tomaselli 2003) and were in accordance with previous findings in adults with repaired EA (Biller 1987, Tovar 1995, Tomaselli 2003). However, the manometric findings among patients with columnar epithelial metaplasia differed markedly from those with normal histology or esophagitis only. The patients with epithelial metaplasia showed significantly lower median wave amplitudes in the distal esophagus as well as decreased frequency of propagating peristalsis. Weak contractions of the distal esophagus and impaired peristalsis associate with impaired esophageal clearing capacity (Mittal 2004, Tovar 1995, Kawahara 2007), which may in turn predispose to GER and development of epithelial metaplasia (Lambert 2007). Based on a logistic regression model, age and several anastomotic complications including surgically treated anastomotic stricture in infancy, recurrent tracheoesophageal fistula, myotomy of the upper esophageal pouch, and anastomotic stricture in adulthood were, in addition to low esophageal distal wave amplitudes and non-propagating peristalsis, strong predictive factors for epithelial metaplasia. Thus, primary esophageal anastomosis under considerable tension and repeated, often extensive, surgical dissection during re-operations may result in additional neuromuscular damage and predispose to further impairment in esophageal motility, to GER and to subsequent development of epithelial metaplasia.

This was a large population-based series of 101 adults with repaired EA with quite uniform results justifies application of these results to adults with repaired EA in the entire study population. Additionally, our main results are in accordance with results on esophageal morbidity (Krug 1999, Deurloo 2003, Deurloo 2005, Taylor 2007), and function (Orringer 1977, Tovar 1995, Tomaselli 2002, Kawahara 2007). Most studies on long-term outcomes of EA have included only symptomatic patients, whereas this population-based study included also those without symptoms.

RESPIRATORY MORBIDITY

To the best of our knowledge, this is the largest and the only population-based study on respiratory morbidity and PF in adults with repaired EA. We found an increased incidence of daily respiratory symptoms and asthma as well as decreased respiratory symtom-related quality of life. PF abnormalities were detectable in 78% of the patients: restriction in 57%, obstruction in 55%, and both these ventilation defects in 36%. Occurrence of restrictive PF after repair of EA was associated with thoracotomy-induced rib fusion, which was present in one-third, and GER-associated esophageal epithelial metaplasia in one-fifth of the patients. However, the restrictive ventilation defect showed no association with current respiratory symptoms.

In Finland, the DDA prevalence among children is 8.8% (Von Herzen 2006), and among adults 6% (Pallasaho 2002). The prevalence is higher in EA patients (LeSouëf 1987, Sompppi 1998, Agrawal 1999, Taylor 2007, Malmström 2008). In the present study, 16% of the adult patients with repaired EA and 6% of the general population-derived controls had DDA, figures in line with those of other reports (LeSouëf 1987, Somppi 1998, Agrawal 1999, Taylor 2007, Malmström 2008). Wheeze occurred in 37% of the patients and in 30% of the controls. Self-reported wheeze usually occurs in X% to 37% of the survivors of EA with no tendency toward improvement with age (Chetcuti 1988-1993, Somppi 1998, Agrawal 1999, Goyal 2006).

The occurrence of respiratory symptoms was clearly lower among the present adult study population than in children and adolescents with repaired EA (Chetcuti 1988, Somppi 1998, Taylor 2007, Malmström 2008), suggesting that with age, prevalence of respiratory problems decreases. Nevertheless, lower respiratory symptom-related quality of life and daily respiratory symptoms were still significantly more common among patients than among controls. Incidence of asthma and of BHR was in line with others´ findings, whereas the PF abnormalities were more common among our adults than among children and adolescents (Milligan 1979, Couriel 1982, Chetcuti 1992, Robertson 1995, Agrawal 1999, Malmström 2008), which is in accordance with other findings among adults (Biller 1987). The DDA prevalence was similar to that found earlier for patients with repaired EA (LeSouëf 1987, Somppi 1998, Agrawal 1999, Taylor 2007, Malmström 2008), but was significantly higher than in the general population (Von Hertzen 2006).

Prevalence of BHR in the general Finnish population with no previous diagnosis of asthma or chronic bronchitis and with normal lung volumes is 17% (Juusela 20008). In our study population, BHR occurred markedly more frequently, in 41%, which is in accordance with other studies' findings (Milligan 1979, Robertson 1995, Ekroos 2000, Malmström 2008). It has been postulated that increased bronchial reactivity in these patients would merely reflect sequalae of chronic lung disease from airway epithelium damaged by recurrent aspiration of acidic gastric contents (Milligan 1979). Severe or moderate BHR has been associated with a more restrictive ventilatory defect among adolescents (Malmström 2008), but no correlation has emerged between increased BHR and history of asthma or atopic eczema (Robertson 1995, Malmström 2008). In the present study, BHR was associated with current respiratory symptoms and atopy. Atopy prevalence was 37%, and 22% had multiple sensitization, in accordance with incidences of 34 to 47% and 16 to 42% among the general population (Pallasaho 2006).

Increased exhaled nitric oxide (FE^{NO}) is associated with the steroid-responsive eosinophilic airway inflammation that is higher particularly in patients with atopic asthma (Taylor 2006). In one study, elevated FE^{NO} was detectable in 23% of the adolescents with repaired EA. Elevated values were detectable only in patients with atopy and increased BR, but with no relation to respiratory symptoms (Malmström 2008). Among the present study population, elevated FE^{NO} occurred in 11%. FE^{NO} was associated with neither current respiratory symptoms, tendency to atopy, nor pulmonary abnormalities. In short, in adult patients with repaired EA, in the absence of atopy, airway inflammation was uncommon.

The proportion of children and adolescents with repaired EA having a restrictive PF defect has been reported to range from 21 to 40%, and an obstructive ventilation defect from 16 to 54% (Milligan 1979, Couriel 1982, Chetcuti 1992, Robertson 1995, Malmström 2008). Our respective figures were 57% and 55%. PF abnormalities have shown no correlation with respiratory or esophageal symptoms (Chetcuti 1992, Robertson 1995, Malmström 2008). Although a clear link exists between severity of GER and persistence of respiratory symptoms among EA survivors (Goyal 2006), the reason for PF abnormalities is unclear. They have been suggested to result from recurrent aspiration (Chetcuti 1992), from poor tracheal clearance, this leading to recurrent episodes of bronchitis, and of pneumonia leading to lung damage (LeSouëf 1987, Robertson 1995), or from poor lung growth during infancy (Milligan 1979). In the present study, thoracotomy-induced rib fusion and GER-associated epithelial metaplasia of the esophagus were significant predictors of restrictive ventilation defect. Thus, epithelial metaplasia served as a surrogate marker for significant GER, which may result in repeated aspiration and lung damage. On the other hand, rib fusion leads to an immobile and thus restrictive thoracic cage.

After repair of EA, respiratory morbidity extends into adulthood in a significant number of patients. Respiratory symptoms such as aspiration, choking, wheezing, persistent cough, repeated respiratory infections, and asthma, as reported earlier (LeSouëf 1987, Chetcuti 1992, Chetcuti 1993, Kovasi 2004, Malmström 2008), were also common in our study population. We found that adults with repaired EA have significantly more respiratory symptoms, infections, asthma, and allergies than do general population-derived controls. The prevalence of asthma among adults with repaired EA was significantly higher. Restrictive ventilatory defect was associated with thoracotomy-induced rib fusion and primary surgical complications predisposing to gastroesophageal reflux-associated esophageal epithelial metaplasia in adulthood.

MUSCULOSKELETAL DEFECTS

Several studies have reported the incidence of vertebral and other skeletal anomalies associated with EA to range between 9 and 24% (Sparey 2000, Keckler 2007, Durning 1980, Gillsanz 1983, Dunley 2007, Spitz 2006). In this study, the incidence of vertebral anomalies was markedly higher, 45%, and the combined incidence of vertebral and other skeletal anomalies was 67%. Only 11% of these have been diagnosed during childhood. Our high incidence (38%) of cervical vertebral anomalies in EA patients is a novel finding. In addition, over one-third (34%) of EA patients have Klippel-Feil type cervical vertebral fusions and cervical kyphosis occurring both with and without vertebral anomalies. Fused cervical vertebrae may later in life result in cervical instability and spinal stenosis (Hall 1990, Ritterbusch 1991), although this was not evaluated here. On the other hand, the patients had no symptoms indicating cervical instability or stenosis. Nor have any of our patients had surgery of the cervical spine. Cervical instability is associated with highly increased risk for spinal cord injury and sudden death if left untreated (Kabins 2001). Thus, further assessment of cervical instability with dynamic flexion-extension magnetic resonance imaging in patients with fused vertebrae of the cervical spine may be warranted.

Any other associated anomaly was recorded in one-third of our patients during the primary treatment period or during childhood. Overall incidence of associated congenital malformations was much higher (almost 70%), though vertebral and other skeletal anomalies become evident only later in life when the musculoskeletal system develops. Nowadays, vertebral anomalies and rib anomalies are screened for after birth, but only major anomalies and defects are recognizable in infancy. Skeletal anomalies are common in association with EA: nearly half have vertebral anomalies predominating in the cervical spine, and one-fourth have radial ray anomalies. Cervical vertebral anomalies in over one-third (38%), was a novel finding.

The presence of additional associated anomalies was the most significant risk factor for occurrence of vertebral anomalies. Accordingly, spinal anomalies are associated with several syndromes, associations, and diseases (Louhimo 1983, Engum 1995, Spitz 1996, Sparey 2000, McCollum 2003, Lawhon 1986, Keckler 2007). The connections and mechanisms between these phenomena are unclear, although simultaneous development of different organs during embryogenesis explains the occurrence of multiple anomalies in a single individual. The cervical vertebrae and the esophagus are anatomically adjacent structures, and so a local developmental defect in this area may underpin the synchronous occurrence of these anomalies, as shown for the first time in the present study. The causative factors, however, remain unknown.

At birth, none of the patients had scoliosis evident on chest radiographs. One descriptive series reported 13% of young adolescents with repaired EA having scoliosis, 19% spinal deformities, and 25% anterior chest wall asymmetries (Chetcuti 1989). At the mean age of 36 years, our incidence of scoliosis in clinical assessment was 54% and in radiological examination 56%. No other systematic population-based investigations on the incidence of scoliosis in EA patients seem to exist.

Our findings suggest that the primary EA repair through the posterolateral thoracotomy frequently (30%) resulted in rib fusions, and these were major contributors to the later scoliosis. Thoracotomy in infancy for various reasons has been reported to cause scoliosis in 4% to 50% of cases (Kawakami 1995, Bal 2003, Westfelt 1991). In addition, 27% of patients with congenital diaphragmatic defects develop scoliosis (Vanamo 1996). Surgical trauma to the thoracic cage has been regarded as the main cause of scoliosis in these patients. In accordance with this, an association between surgically corrected congenital heart defects and scoliosis is well established, and most of these cases involve scoliosis without any morphological abnormality in the vertebral column (Beals 1972, Beneaux 1976, Coran 1999). One-third of patients with congenital heart disease have developed scoliosis also after median sternotomy (Ruiz-Iban 2005). In the present study, left thoracic was the most common type of scoliosis in EA patients without synchronous vertebral anomalies, differing strikingly from the typical right thoracic of the idiopathic scoliosis curve (Weinstein 2001). The natural history of EA-associated scoliosis seems rather benign, since none of the patients had needed scoliosis surgery. Whether a thoracoscopic approach reduces the thoracotomy-induced rib fusions and development of thoracic scoliosis remains unclear (Holcomb 2005, Rothenberg 2005, Lima 2007).

Jaureguizar (1985) reported that 24% of the children with repaired EA have “winged” scapula, and 20% have anterior chest wall deformities. Cherup (1986) noted rib fusions and female breast disfigurement requiring plastic surgery in some cases after repair of EA. Chetcuti (1988) supports these findings with a 20% occurrence of anterior chest wall deformities after EA repair. In our study, 15% of the adults with repaired EA had anterior chest wall deformities, one-fifth had limited range of motion of the right upper extremity, nearly one-third had rib fusions, and over half had scoliosis in adulthood.

Conclusions

Significant esophageal and respiratory morbidity associated with EA extends into adulthood. Esophageal symptoms are common among adults with repaired EA. No association exists between the esophageal symptoms and histological findings. Esophageal motility disturbances as well as columnar epithelial metaplasia are common in adults with repaired EA. Esophageal anastomotic complications may further promote esophageal dysmotility and GER, which together with increasing age predispose to development of esophageal columnar metaplasia. Considering the relatively young age of the survivors, further studies and continued follow-up are warranted to elucidate the risk for esophageal cancer after repair of EA. The overall cancer incidence did not differ from that of the general Finnish population. According to our data, risk for esophageal cancer was less than 500-fold that of the general population.

Adults with repaired EA have significantly more respiratory symptoms and infections as well as asthma and allergies when compared to figures for the general population. Obstruction and asthma are not the main problems in adulthood. Instead, BHR and restrictive ventilatory defect rise in frequency. Respiratory-related morbidity and impaired PF extend into adulthood after repair of EA in a significant number of patients. Nearly half the patients had BHR.

Thoracotomy-induced rib fusion and GER-associated columnar metaplasia were the strongest risk factors for restrictive ventilatory defect, which occurred in over half the patients, and over half the patients with repaired EA will develop scoliosis. Risk for scoliosis is 13-fold after repair of EA in relation to risk in the general population. Nearly half the patients have vertebral anomalies predominating in the cervical spine. Of these, most were vertebral fusions, and most of these deformities went undiagnosed during the initial treatment period or during growth. However, the natural history of spinal defects seems rather benign, and spinal surgery is rarely indicated.

Key points

Gastroesophageal and respiratory morbidity and musculoskeletal defects are common in adulthood after repair of EA (Figure 14). Primary surgical complications predicted occurrence of esophageal epithelial metaplasia with increasing age. Primary anastomotic complications such as early stricture, anastomotic leak, and recurrent fistula had marked effects on long-term outcomes, and therefore primary complications should be minimal. Surgical complications may predispose to esophageal dysmotility and GER with its complications. Because esophageal symptoms of GER and dysphagia bore no relationship to esophageal epithelial alterations, surveillance should not be based on symptoms alone.

Reflux esophagitis and esophageal columnar metaplasia that commonly associate with EA are risk factors for esophageal adenocarcinoma. Although only six case reports describe esophageal cancer among young adults with repaired EA worldwide, no cases of esophageal cancer emerged among our study population, and our overall cancer incidence did not differ from that of the general population.

Respiratory symptoms had no correlation with clinical findings in PFT. Although many had restrictive ventilatory defect in adulthood, most of these defects were mild.

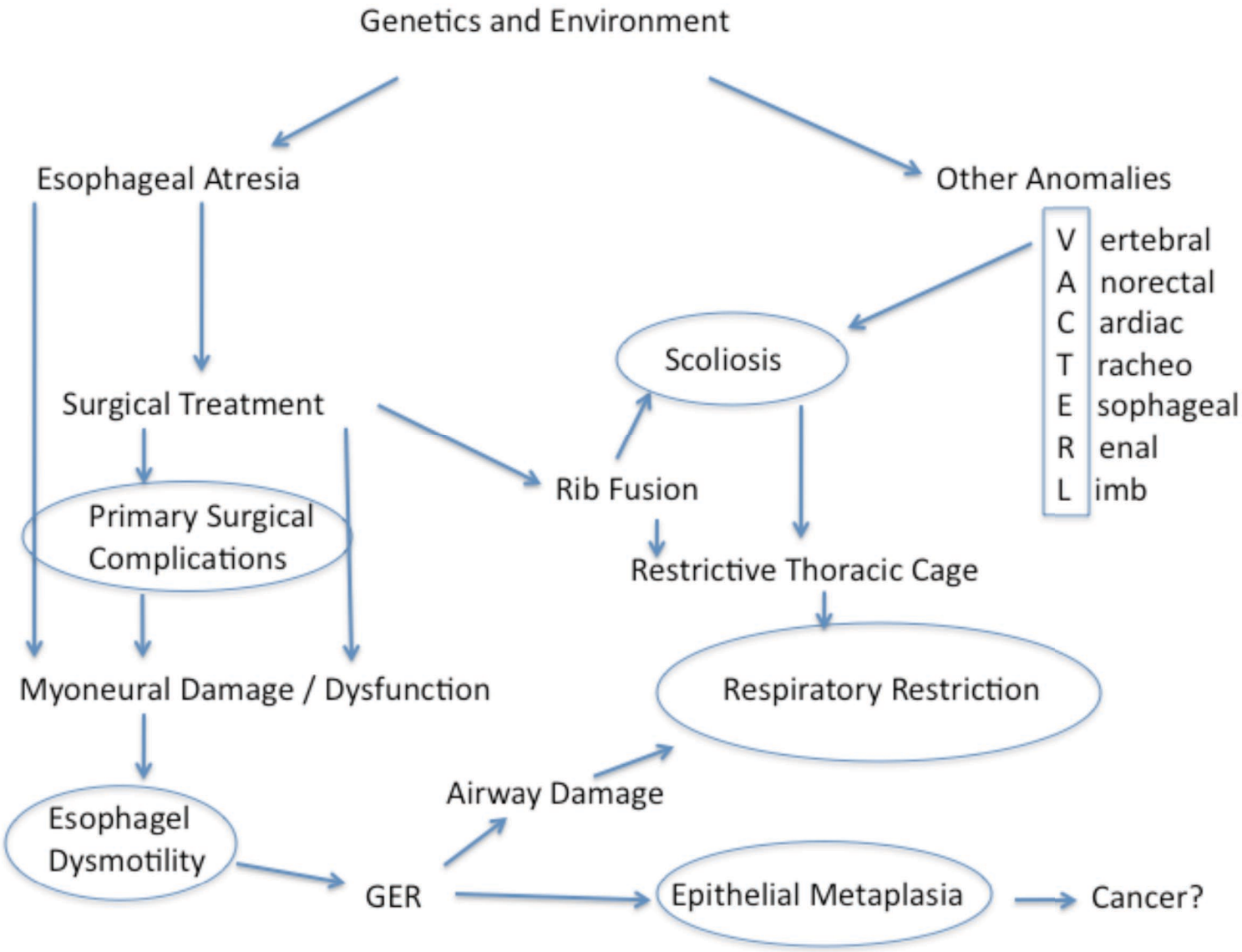
Over two-thirds of the patients with EA had associated anomalies, and nearly a quarter had VACTERL multianomaly association. Musculoskeletal defects after repair of EA were common. Over half developed scoliosis, and nearly half had vertebral anomalies, predominating in the cervical spine in over one-third of the patients. Radial ray anomalies were evident in one quarter.

Future considerations

An endoscopic surveillance study among the participants with esophageal epithelial metaplasia is necessary. Esophageal epithelial changes will be further analyzed with gene expression profile analysis to assess potential risk for esophageal cancer. Health-related quality of life evaluation in relation to symptoms is also an interesting aspect of the long-term outcome of EA.

Over one-third had cervical vertebral anomalies, ones which might lead to cervical instability, and therefore an instability study of the cervical spine would be of interest. Because one-quarter of our patients with EA had radial ray anomalies, we will evaluate thumb and other radial ray anomalies in association with EA.

Figure 14 Illustration of long-term outcomes of esophageal atresia.



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