Perinatal Risk Factors for Cancer of the Esophagus and Gastric Cardia: A Nested Case-Control Study

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Abstract

Background: **We have previously hypothesized that preterm birth or impaired fetal growth may cause esophageal adenocarcinomas through gastroesophageal reflux early in life. In this study, we aimed to test if there is an association between gestational duration and birth weight on the one hand, and risk of esophageal and cardia adenocarcinoma on the other.**

Methods: **We conducted a nested case-control study of 67 cases of esophageal adenocarcinoma and 93 cases of cardia adenocarcinoma, whereas 50 cases of squamous cell carcinoma were studied for comparison. Birth records of cases were traced. Three matched controls per case were randomly selected. Perinatal data were extracted from birth records.**

Results: **Long gestational duration was associated with a decreased risk of cardia adenocarcinoma (P_{trend} = 0.001) and a nonsignificant decreased risk of esophageal adenocarcinoma (P = 0.07), whereas no such association was found for esophageal squamous cell carcinoma (P = 0.96). Birth weight was not associated with risk of any of the studied cancers. Compared with lower maternal age (≤24 years) at giving birth, maternal age of 25 to 29 years were associated with a decreased risk of esophageal adenocarcinoma and squamous cell carcinoma (odds ratio, 0.4; 95% confidence interval, 0.2-0.9 and odds ratio, 0.3; 95% confidence interval, 0.1-0.8, respectively).**

Conclusions: **Numerical constraints hamper inference, but our results are somewhat consistent with the idea that future risk of esophageal and cardia cancer may in part be determined already perinatally or in infancy and give some limited support to the hypothesis that timing of birth influences risk.** (Cancer Epidemiol Biomarkers Prev 2006;15(5):867–71)

Introduction

The incidence of esophageal adenocarcinoma has increased rapidly in many populations, whereas the occurrence of squamous cell carcinomas has remained relatively stable (1, 2). In the United States, for example, the incidence of adenocarcinomas has risen >6-fold since the 1970s, and thus surpassed the occurrence of squamous cell carcinomas (2). Accordingly, the etiologies of the two types cannot be identical. Whereas smoking and alcohol consumption are dominating risk factors for squamous cell carcinoma in Western populations, gastroesophageal reflux and high body mass index are the most prominent risk indicators for adenocarcinomas (1, 3). Although the prevalence of obesity has increased, potentially thus explaining part of the surge in adenocarcinomas, the rapidity of increase and the ~7-fold male predominance implicate that some other yet unknown factor is operating (4).

Recently, we found an unexpectedly high incidence of esophageal cancer, notably adenocarcinomas, in a cohort of individuals born preterm or small for gestational age (5). The finding was not anticipated *a priori* and was based on few cases, but because gastroesophageal reflux is common among neonates, particularly those born preterm or small for gestational age (6), we hypothesized that preterm birth or fetal growth retardation may cause esophageal adenocarcinomas through exposure of regurgitated stomach content to the immature esophageal mucosa of the newborn.

As a first test of this hypothesis, we have used prospectively recorded information in old birth records to conduct a population-based nested case-control study of perinatal exposures and risk of esophageal adenocarcinoma. Because tumors classified as cardia adenocarcinomas seem to be, at least partly, a distinct etiologic entity (3, 7-10), we studied cardia adenocarcinomas separately, whereas esophageal squamous cell carcinomas were included for comparison only.

Materials and Methods

Identification of Cases and Controls. The study base of this population-based case-control study was the person-time experienced between December 1, 1994, through December 31, 1997, among persons born in Sweden in 1916 onward who had retrievable birth records from the time of their birth. In Sweden, the proportion of hospital births, and thus the proportion of individuals with birth records, during the period in which the source population was born, rose steadily, from ~15% in 1915, to 75% in 1930, 95% in the late 1940s, and close to 100% in the 1950s (11, 12).

By law, birth records have to be kept, together with information from the antenatal care, in archives of all delivery units in Sweden. Although the organization of records has varied over time and between counties, they have generally been stored systematically and can be traced using the individually unique National Registration Number, assigned to all residents and used as identifier in virtually all Swedish registries and archives.

We took advantage of the comprehensive case-finding effort of a nationwide population-based case-control study (3) conducted in Sweden during a time period that coincided with the time window of follow-up in the present study. Eligible as cases in the present study were subjects contributing to the study base described above and who were

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diagnosed with a new adenocarcinoma of the esophagus or gastric cardia in the studied time window. For comparison, we included cases of esophageal squamous cell carcinoma, but because they were in majority during the period of case ascertainment, we restricted their source population to individuals born on even-numbered days.

To find the cases' birth-record archives, we collected information about the place of birth from the Population Register at the Swedish tax authority for all 618 patients included in the original case-control study. At the birth-record archives, we manually scrutinized the ledgers and/or the record binders, generally sorted on date of admission, to identify each case's birth record. Of the 618 case patients in the original study, 210 (34%) had traceable birth records and thus belonged to the source population of the present study.

All cases were uniformly investigated, classified, and documented according to the protocol for the original case-control study, and considerable effort was made to distinguish between different tumor types (3). Ninety-seven percent of the cases' tumor specimens were reviewed by a single pathologist.

Control Subjects. The first three singleton offspring of the same sex born after a case subject in the same ward represented potential control subjects. To verify that a potential control subject was alive and had not been diagnosed with esophageal cancer at the time of the corresponding case's diagnosis, we examined records at the parish of residence and, on the basis of the national registration number, at the Swedish Death Registry and the Swedish Cancer Registry. Out of 630 potential selected persons, 156 were excluded because they had died (but none was diagnosed with esophageal or cardia cancer), leaving 474 control subjects (75%) to be included in the analysis.

Measurement of Exposure. The following information in the birth records was extracted and computerized: maternal and paternal age, father's profession, maternal age at menarche, previous miscarriages, proteinuria during pregnancy or postpartum, birth order of index child, gestational age at birth, birth weight, birth length, placental weight, neonatal jaundice, breast feeding at discharge, and duration of postpartum stay at hospital.

Gestational age at birth was recorded as number of complete weeks of gestation at birth. We evaluated socioeconomic status according to the father's or single mother's education level by use of the following categories: high (college education), medium (white-collar worker or farm owner with no college education), and low (blue-collar worker or farmhand). Because there were only 10 subjects in the highest category of socioeconomic status, high and medium were combined to one category.

Data Analysis. Data were modeled through conditional logistic regression, stratified by sex and birth year and follow-up time in 5-year groups. Throughout, analyses were run separately for esophageal adenocarcinoma, cardia adenocarcinoma, and esophageal squamous cell carcinoma. Variables were kept in the final regression models if they were independently associated with the outcome or confounders or if they improved the model fit significantly. Models were compared using the likelihood ratio test.

Gestational age and birth weight were categorized into quartiles. For socioeconomic status, there were missing data in one third of the subjects. Therefore, to avoid considerable loss of statistical power, this variable was left out from the final models. However, among the subjects with information on socioeconomic status, introduction of this variable into the model had no substantial effect on the other estimates.

Birth weight is highly dependent on gestational duration, and to improve the interpretability of this variable and separate fetal growth from gestational duration, a score (z score) for birth weight standardized for gestational age at birth was calculated using the following formula:

$$\text{Birth weight score} = (\text{[subject's birth weight} - \text{mean birth weight in that gestational week]}/\text{standard deviation of birth weight in that gestational week})$$

To evaluate whether any potential association with gestational age at birth was different for males and females, and for different ages at diagnosis, we reran the analyses stratified by these variables. Tests for homogeneity of odds ratios in these analyses were done by likelihood ratio test, comparing nested models with and without interaction terms. Tests for trend were done by introducing the variables into the models in their noncategorized, continuous, or ordinal form.

All P values were derived from two-tailed tests. Analyses were done using Intercooled Stata 8.1 for Microsoft Windows.

Results

Included in the study were 67 patients with adenocarcinoma of the esophagus, 50 patients with squamous cell carcinoma of the esophagus, and 93 patients with adenocarcinoma of the gastric cardia. The age and sex distributions among the case patients are presented in Table 1.

Gestational age at birth was negatively associated with risk of adenocarcinoma of the gastric cardia (P_{trend} = 0.001), with an ~3-fold gradient between the extreme categories (≤38 versus ≥41 weeks of gestation). A similar but weaker and nonsignificant negative association was also seen with esophageal adenocarcinoma risk (P_{trend} = 0.07), but the trend was not entirely consistent. For both cancer sites, the steepest gradient in risk was between being term and being postterm. No such association was found for esophageal squamous cell carcinoma (P_{trend} = 0.96). There were no

Table 1. Characteristics of case patients by histologic type of cancer

Variable	Adenocarcinoma of the esophagus	Adenocarcinoma of the gastric cardia	Squamous cell carcinoma of the esophagus
No. cases	67	93	50
Sex			
Female	8 (12%)	15 (16%)	16 (32%)
Male	59 (88%)	78 (84%)	34 (68%)
Age at diagnosis			
Mean (range)	61.8 (41-79)	60.2 (32-79)	62.1 (42-78)
>55	21 (31%)	32 (34%)	11 (22%)
56-65	20 (30%)	26 (28%)	22 (44%)
66+	26 (39%)	35 (38%)	17 (34%)

Table 2. Results of univariate analysis

Variable	Controls (%)	Adenocarcinoma of the esophagus		Adenocarcinoma of the gastric cardia		Squamous cell carcinoma of the esophagus	
		Cases (%)	OR (95% CI)*	Cases (%)	OR (95% CI)*	Cases (%)	OR (95% CI)*
Maternal age, y							
≤24	127 (27%)	28 (42%)	1	24 (26%)	1	19 (40%)	1
25-29	154 (33%)	14 (21%)	0.4 (0.2-0.7)	26 (29%)	1.0 (0.5-1.8)	14 (29%)	0.5 (0.2-1.0)
≥30	185 (40%)	24 (36%)	0.6 (0.3-1.0)	41 (45%)	1.2 (0.7-2.0)	15 (31%)	0.5 (0.2-1.0)
Missing data	8	1		2		2	
Parental socioeconomic class							
High (1 + 2)	96 (30%)	9 (23%)	0.7 (0.3-1.7)	11 (17%)	0.4 (0.2-0.8)	7 (20%)	0.8 (0.3-1.9)
Low (3)	223 (70%)	30 (77%)	1	54 (83%)	1	28 (80%)	1
Missing data	155	28		28		15	
Birth order							
1	192 (%)	32 (48%)	1	34 (36%)	1	21 (42%)	1
2	128 (%)	17 (25%)	0.8 (0.4-1.6)	22 (24%)	0.9 (0.5-1.6)	16 (32%)	1.2 (0.6-2.4)
3+	154 (%)	18 (27%)	0.7 (0.4-1.2)	37 (40%)	1.3 (0.7-2.1)	13 (26%)	0.8 (0.4-1.7)
Missing data	—	—		—		—	
Gestational age at birth, wk							
≤38	111 (25%)	15 (25%)	1.1 (0.5-2.5)	30 (34%)	1.3 (0.7-2.3)	14 (30%)	1.7 (0.7-4.5)
39	105 (24%)	24 (41%)	1.9 (0.9-4.0)	26 (30%)	1.0 (0.5-2.0)	12 (25%)	1.6 (0.6-4.4)
40	98 (22%)	12 (20%)	1	22 (25%)	1	7 (15%)	1
≥41	129 (29%)	8 (14%)	0.5 (0.2-1.4)	10 (11%)	0.4 (0.2-0.8)	14 (30%)	1.6 (0.6-4.2)
Missing data	31	8		5		3	
Relative birth weight †							
1st quartile	112 (26%)	17 (29%)	1	19 (22%)	1	10 (21%)	1
2nd quartile	112 (26%)	13 (22%)	0.8 (0.4-1.8)	20 (23%)	1.1 (0.6-2.2)	13 (27%)	1.3 (0.5-3.0)
3rd quartile	107 (24%)	18 (30%)	1.1 (0.6-2.3)	21 (24%)	1.1 (0.6-2.3)	12 (26%)	1.3 (0.5-3.0)
4th quartile	107 (24%)	11 (19%)	0.7 (0.3-1.7)	27 (31%)	1.4 (0.7-2.7)	12 (26%)	1.3 (0.6-3.2)
Missing data	36	8		6		3	

Abbreviations: OR, odds ratio; 95% CI, 95% confidence interval.
*Odds ratios were inherently adjusted for the matching variables, sex, and birth year.
†Birth weights were standardized for gestational week and then divided into quartiles.

associations between birth order or relative birth weight and risk of any of the tumors.

High or medium paternal socioeconomic status compared with low was inversely associated with risk of all three histologic types, but only significantly so for adenocarcinoma of the gastric cardia (odds ratio, 0.3; 95% confidence interval, 0.1-0.6; Table 3). It should be noted that information on paternal occupation was missing for one third of the subjects.

Compared with maternal age at giving birth of up to 24 years, higher maternal age was associated with a 2- to 3-fold decrease in risk of esophageal adenocarcinoma and squamous cell carcinoma, but the trend was monotonic across all age categories only for squamous cell carcinoma. No such relation was evident for cardia adenocarcinoma (Table 3). There was no clear association between birth order and any of the tumor types. The variable was, however, kept in the

Table 3. Results of multivariable analysis

Variable	Adenocarcinoma of the esophagus		Adenocarcinoma of the gastric cardia		Squamous cell carcinoma of the esophagus	
	OR* (95% CI)	P †	OR* (95% CI)	P †	OR* (95% CI)	P †
Maternal age, y						
≤24	1		1		1	
25-29	0.4 (0.2-0.9)		0.9 (0.5-1.8)		0.3 (0.1-0.8)	
≥30	0.6 (0.3-1.4)	0.14	1.0 (0.5-2.0)	0.15	0.3 (0.1-0.8)	0.23
Parental socioeconomic class						
High (1 + 2)	0.7 (0.3-1.7)		0.3 (0.1-0.6)		0.5 (0.2-1.6)	
Low (3)	1		1		1	
Birth order						
1	1		1		1	
2	0.9 (0.4-1.9)		0.8 (0.4-1.6)		1.6 (0.7-3.6)	
3+	0.9 (0.4-2.1)	0.79	1.3 (0.7-2.5)	0.44	1.6 (0.6-4.2)	0.24
Gestational age at birth, wk						
≤38	1.2 (0.5-2.7)		1.3 (0.7-2.4)		1.6 (0.6-4.2)	
39	1.8 (0.8-3.8)		1.1 (0.6-2.1)		1.4 (0.5-4.1)	
40	1		1		1	
≥41	0.6 (0.2-1.5)	0.07	0.4 (0.2-0.8)	0.001	1.5 (0.6-4.0)	0.96
Relative birth weight ‡						
1st quartile	1		1		1	
2nd quartile	0.9 (0.4-1.9)		1.0 (0.5-2.1)		1.0 (0.4-2.5)	
3rd quartile	1.3 (0.6-2.8)		1.1 (0.5-2.1)		1.3 (0.5-3.2)	
4th quartile	0.8 (0.3-1.8)	0.97	1.2 (0.6-2.3)	0.40	1.5 (0.6-3.8)	0.22

*All variables were adjusted for sex, birth year, maternal age, birth order, duration of gestation, and birth weight.
†P value for trend. Tests for trend were done by introducing the variables in their noncategorized, continuous, or ordinal form.
‡Birth weight relative to gestational age at birth.

Table 4. Results of analyses of the association with gestational age at birth, stratified by attained age at diagnosis

	Adenocarcinoma of the esophagus		Adenocarcinoma of the gastric cardia		Squamous cell carcinoma of the esophagus	
	Cases	OR* (95% CI)	Cases	OR* (95% CI)	Cases	OR* (95% CI)
Unstratified OR*	67	0.9 (0.8-1.0)	93	0.8 (0.7-0.9)	50	1.00 (0.87-1.16)
Age at diagnosis						
≤55	21	0.7 (0.6-1.0)	32	0.7 (0.6-0.9)	11	0.9 (0.7-1.3)
56-65	20	0.8 (0.7-1.1)	26	0.8 (0.7-1.0)	22	1.0 (0.8-1.3)
≥66	26	1.0 (0.8-1.2)	35	0.8 (0.7-1.0)	17	1.0 (0.8-1.3)

NOTE: Birth weight was relative to gestational age at birth.
*Odds ratio per 1 week increase in gestational age at birth. All variables were adjusted for sex, birth year, maternal age, birth order, and birth weight.

final model because of its confounding effect on maternal age, birth weight, and gestational duration.

When data were stratified by attained age at diagnosis, the inverse associations with gestational age at birth seemed somewhat stronger for both adenocarcinoma subtypes among those diagnosed at an early age (Table 4). Test for homogeneity of odds ratios were, however, not significant: P for homogeneity across strata of attained age was 0.82 for adenocarcinoma of the esophagus, 0.46 for adenocarcinoma of the gastric cardia, and 0.47 for squamous cell carcinoma of the esophagus.

We found no association with paternal age (81% missing data), maternal age at menarche (77% missing), previous miscarriages (4% missing), proteinuria during pregnancy (68% missing), proteinuria on arrival to maternity ward (3% missing), proteinuria during postpartum stay (60% missing), neonatal jaundice (25% missing), breast feeding (50% missing), and duration of postpartum stay (no missing data; data not shown).

Discussion

Although our present result did not perfectly coincide with the ones reported previously (5), they provide some further evidence that future risk of esophageal and cardia cancer may, in part, be determined perinatally. Specifically, they give some limited support to the hypothesis that timing of birth is associated with risk of esophageal and cardia adenocarcinomas. No association was found between gestational duration and risk of esophageal squamous cell carcinoma, and there was no indication of an association between relative size of infant at birth and risk of any of the studied tumors.

With less than a hundred cases of each tumor type, the risk of spurious association is rather high; all interpretation of the positive findings in the present study should be done bearing in mind that chance, alone or in part, may explain our associations. To our knowledge, our recently published follow-up of a cohort of individuals born preterm (5) is the only previous study assessing perinatal variables in relation to risk for esophageal cancer.

The strengths of our study include the use of prospectively registered exposure data to assess perinatal variables and the uniform classification of tumors. The main limitation is, apart from the low statistical power, the narrow range of exposure. In our hypothesis-generating cohort study, we followed-up an exceptionally large number of babies born before 35 weeks of gestation and/or small for gestational age and found a 7-fold increased risk of esophageal adenocarcinoma compared with the general population. The finding was, however, based on only four cases because esophageal adenocarcinoma is a rare outcome. In the present case-control study, we have considerably more cases; on the other hand, few of them were born preterm. Nevertheless, despite the differing ranges of exposure in this study and the previous one, both studies present associations between risk of esophageal and cardia adenocarcinoma and gestational duration that deserve further attention.

The source population for our study was restricted to individuals with retrievable birth records. This source population generated both the cases and the individually matched controls. Hence, any selection bias associated with unavailability of birth records affects the generalizability rather than the internal validity. Sixty percent of the cancer cases who were diagnosed among native Swedes during the case ascertainment period did not belong to the restricted source population of persons with retrievable birth records. Because birth at home was one of the major reasons for the absence of records and home births were more common in rural than in urban areas, studied patients grew up in urban areas more often than did patients who were left out of the study. Because hospital care was entirely public and tax funded, with equal access for everybody, there was virtually no selection with respect to socioeconomic class. The cases studied did not differ importantly from those left out of the study with regard to age at diagnosis, sex distribution, SES at diagnosis, distribution of tumor types, or tumor stage (data not shown).

In our previous article (5), we suggested that the increased frequency of reflux among preterm babies could be a mechanism behind our finding. The association observed in the present investigation, this time admittedly more with cardia cancer than with esophageal adenocarcinoma, was driven mainly by a substantially lower risk among individuals born postterm compared with term. The reflux argument, therefore, is less persuasive. Inarguably, gastroesophageal reflux is common among preterm infants (6, 13). The predominant mechanism—transient relaxation of the lower esophageal sphincter (13)—is the same as in adults, and the resting pressure of the lower sphincter is typically well above the level that is needed for preventing passive regurgitation (14). Gastroesophageal reflux occurs, however, in healthy babies born at term as well (15). In fact, neither the rate of occurrence of transient relaxation of the lower esophageal sphincters (16) nor the prevalence of gastroesophageal reflux, ascertained by esophageal pH monitoring (17), varied significantly with gestational age across preterm and term in two independent investigations. If anything, one of the studies found that the number of episodes with pH <4 during 24 hours was greater in the term compared with the preterm infant group (17). Hence, there are no indications that babies born term or slightly postterm have any advantages from a reflux perspective. Therefore, other mechanisms must likely be sought for the observed ''protection'' against esophageal and cardia adenocarcinoma afforded by postterm birth. For example, it seems conceivable that the esophageal cell lining is more prepared to be exposed to the acidic stomach content among those born postterm. Given that reflux does not vary across gestational age groups, the epithelium may be less susceptible to the carcinogenic development that potentially is initiated by the reflux of stomach content.

The most highly significant association in the present study was that on risk of adenocarcinoma of the gastric cardia, not on esophageal adenocarcinoma, for which our prior hypothesis was primarily forwarded. However, the gastroesophageal junction does not divide the adenocarcinomas in the gastro-esophageal area into distinct etiologic categories (7), and analytic studies on cardia adenocarcinomas have suggested that tumors below and above the junction are in part similar (3, 8, 9, 18). Therefore, we included cardia adenocarcinomas into the present study. We had no strong *a priori* hypothesis as to where in the esophagus the effect of prematurity would be strongest. However, we speculated that reflux in the neonate mediated the association and because reflux is by far a stronger risk factor for esophageal adenocarcinoma, we had anticipated a stronger finding for that diagnosis in this analysis. It should, however, be noted that we had 40% more cases of cardia cancers and thus more statistical power to analyze this tumor.

In the analysis stratified by attained age at follow-up, or age at diagnosis, we found a stronger association between gestational duration and esophageal adenocarcinoma among those who were younger, although the statistical interaction testing was not significant. It is highly plausible that risk factors operating perinatally have stronger influence on early onset disease, but much larger studies are required to address this issue.

Apart from the association with gestational duration, we found other indications of perinatal influences on risk for esophageal and cardia cancer. For all three tumor types, there was a decreased risk associated with high socioeconomic status, although only significantly so for cardia adenocarcinoma. This is in all instances in line with previous reports, although available studies have evaluated the status of the index subject, not that of the family of origin (1, 8). Furthermore, we found an association between having a young mother and risk for esophageal cancer, adenocarcinoma, as well as squamous cell carcinoma. At present, we cannot put forward any strong candidate exposure or mechanism to explain this association.

In conclusion, we present new suggestive evidence of associations between perinatal factors and risk for cancer of the esophagus and cardia. First, these findings need to be confirmed in other studies. Second, the mechanisms remain to be explored.

References

1. Nyrén O, Adami H-O. Esophageal cancer. In: Adami H-O, Hunter DJ, Trichopoulos D, editors. Textbook of cancer epidemiology. Oxford, New York (New York): Oxford University Press; 2002. p. 137–54.
2. Pohl H, Welch HG. The role of overdiagnosis and reclassification in the marked increase of esophageal adenocarcinoma incidence. J Natl Cancer Inst 2005;97:142–6.
3. Lagergren J, Bergstrom R, Lindgren A, Nyren O. Symptomatic gastro-esophageal reflux as a risk factor for esophageal adenocarcinoma. N Engl J Med 1999;340:825–31.
4. Lagergren J. Adenocarcinoma of oesophagus: what exactly is the size of the problem and who is at risk? Gut 2005;54 Suppl 1:i1–5.
5. Kaijser M, Akre O, Cnattingius S, Ekbom A. Preterm birth, low birth weight, and risk for esophageal adenocarcinoma. Gastroenterology 2005; 128:607–9.
6. Ewer AK, Durbin GM, Morgan ME, Booth IW. Gastric emptying and gastro-oesophageal reflux in preterm infants. Arch Dis Child Fetal Neonatal Ed 1996;75:F117–21.
7. Dolan K, Morris AI, Gosney JR, Field JK, Sutton R. Three different subsite classification systems for carcinomas in the proximity of the GEJ, but is it all one disease? J Gastroenterol Hepatol 2004;19:24–30.
8. Gammon MD, Schoenberg JB, Ahsan H, et al. Tobacco, alcohol, and socioeconomic status and adenocarcinomas of the esophagus and gastric cardia. J Natl Cancer Inst 1997;89:1277–84.
9. Wu AH, Wan P, Bernstein L. A multiethnic population-based study of smoking, alcohol and body size and risk of adenocarcinomas of the stomach and esophagus (United States). Cancer Causes Control 2001;12: 721–32.
10. Lagergren J, Bergström R, Nyren O. Association between body mass and adenocarcinoma of the esophagus and gastric cardia. Ann Intern Med 1999; 130:883–90.
11. Statistics Sweden. Historical statistics in Sweden. Stockholm: Statistiska centralbyrån (SCB); 1960.
12. Statistics Sweden. Historical statistics in Sweden. Stockholm: Statistiska centralbyrån (SCB); 1955.
13. Omari TI, Barnett C, Snel A, et al. Mechanisms of gastroesophageal reflux in healthy premature infants. J Pediatr 1998;133:650–4.
14. Omari TI, Miki K, Davidson G, et al. Characterisation of relaxation of the lower oesophageal sphincter in healthy premature infants. Gut 1997;40: 370–5.
15. Jeffery HE, Heacock HJ. Impact of sleep and movement on gastro-oesophageal reflux in healthy, newborn infants. Arch Dis Child 1991;66: 1136–9.
16. Omari TI, Barnett CP, Benninga MA, et al. Mechanisms of gastro-oesophageal reflux in preterm and term infants with reflux disease. Gut 2002;51:475–9.
17. Kohelet D, Boaz M, Serour F, Cohen-Adad N, Arbel E, Gorenstein A. Esophageal pH study and symptomatology of gastroesophageal reflux in newborn infants. Am J Perinatol 2004;21:85–91.
18. Farrow DC, Vaughan TL, Sweeney C, et al. Gastroesophageal reflux disease, use of H_2 receptor antagonists, and risk of esophageal and gastric cancer. Cancer Causes Control 2000;11:231–8.