

# Decreasing incidence rate for surgically treated middle ear cholesteatoma in Denmark 1977-2007

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## ABSTRACT

**INTRODUCTION:** The objective was to estimate the annual incidence rate of surgically treated middle ear cholesteatoma (STMEC) in Denmark from 1977 to 2007, taking age, gender and secular trends into consideration.

**MATERIAL AND METHODS:** We used the Danish National Hospital Register to identify all registered cases of STMEC in Denmark between 1977 and 2007. Only the first registration of STMEC (STMEC1) was used for estimation of the annual incidence rate.

**RESULTS:** A total of 13,606 cases of STMEC1 were identified. The highest incidence rates were seen in the beginning of the eighties with a maximum male incidence rate of 14.3 per 100,000 person-years in 1982 and a maximum female incidence rate of 9.1 per 100,000 person-years in 1981. In 2007 the incidence rate per 100,000 person-years was 8.5 for males and 5.4 for females. The age-specific incidence rate peaked at approx. nine years for both males and females with incidence rates of 21.4 and 13.6 per 100,000 person-years, respectively. The male:female incidence rate ratio was 1.51.

**CONCLUSION:** The incidence rate of STMEC1 in Denmark showed a statistically significant decrease from 1977 to 2007. A male predominance was found. The age-specific incidence rate peaked at the age of approx. nine years. Further studies are required to perform a detailed analysis of factors that may influence the incidence rate of STMEC1, e.g. the incidence of grommet insertion and adenoidectomy, antibiotic treatment of middle ear infections and an expanding use of otomicroscopy in the early 1980s.

Studies on the incidence rate of cholesteatoma are relatively sparse. Estimation of the incidence rate is impeded by several factors: a cholesteatoma usually develops slowly which makes it difficult to determine the exact date of the first occurrence; the presence of cholesteatoma can be difficult to determine by otomicroscopy alone; and, finally, as cholesteatoma is a rare disease, epidemiologic studies on cholesteatoma require large study populations.

Previous studies have demonstrated annual cholesteatoma incidence rates ranging from three to 17 per 100,000 person-years [1-6]. These studies were based on questionnaires sent to cholesteatoma surgeons and

departments [1, 2]; on local operation theatre books [4]; and on local surgical and discharge registers [5]. In some of the studies, the exact mechanism for collection of cases was not stated [3, 6].

Population-based health registers can provide valuable information on disease epidemiology provided the register is valid and has a high degree of completeness for the disease studied. For surgically treated middle ear cholesteatoma (STMEC), the validity and completeness of the Danish National Hospital Register (DNHR) were estimated, showing a positive predictive value (PPV) for the first occurrence of STMEC (STMEC1) of 89.3% and a degree of completeness of 89.3% [7].

The aim of the present study was to estimate the incidence rate of STMEC1 in Denmark from 1977 to 2007, taking age, gender, and secular trends into account.

## METHODS

The DNHR contains data on all hospitalisations at Danish hospitals since 1977 and on all outpatients seen since 1995. From 1977 to 1993, the diagnostic information was based on the Danish version of the International Classification of Diseases, 8th revision (ICD-8) [8], and from 1994 and onwards, diagnostic information was based on the International Classification of Diseases, 10th revision (ICD-10) [9]. From 1977 to 1995, surgical information was based on the "Surgical- and Treatment Classification" from the Danish Board of Health [10], and from 1996 on the Danish editions of the "Classification of Surgical Procedures" from the Nordic Medico-Statistical Committee [11].

The selection of relevant diagnostic codes was based on the definition of cholesteatoma provided in Scott-Brown's Otolaryngology, i.e. a squamous, epithelially lined pocket full of squamous epithelial and inflammatory debris which mostly arises in the pars flaccida, but can also occur from a pars tensa retraction pocket [12]. We thus included diagnostic codes for cholesteatoma of the middle ear and mastoid (ICD-8: 387.09; ICD-10: H71 including subgroups, H95.0 and Q16.4A). The codes considered relevant for cholesteatoma surgery included codes concerning mastoidectomy, mastoid obliteration, tympanoplasty, myringoplasty and exploration of the

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middle ear (Surgical- and Treatment Classification: 20380-20700 and 20990; Nordic Classification of Surgical Procedures: all surgical codes starting with KDC, KDD, KDE and KDFD30, except KDCA10, KDCA20, KDCW00, KDEE and KDEE00).

Data on the population were obtained from Statistics Denmark [13]. From 1977 to 2007, the total population of Denmark rose from 5,079,879 to 5,447,084.

The study was approved by the Danish Data Protection Agency.

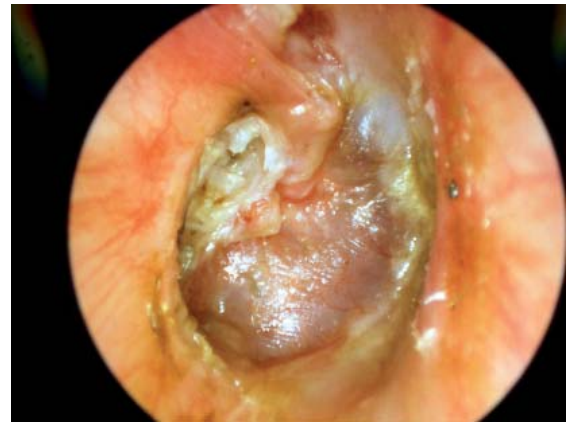
### Analysis

We estimated the incidence rate of STMEC1 using the first occurrence of the cholesteatoma diagnosis combined with any relevant surgery. Annual gender-specific incidence rates were calculated as the number of persons recorded with STMEC1 divided by the population in Denmark. Calculations were performed separately for each gender using figures recorded at the beginning of the calendar year.

Change in the incidence rate over time was examined using linear regression analysis, while the incidence rate ratio for men and women was estimated by the Poisson regression.

The age- and gender-specific incidence rates were calculated by dividing the number of persons of each gender and age recorded with STMEC1 by the population of the same age and gender at the beginning of the calendar year. Subsequently, the mean age- and gender-specific incidence rates for the period were calculated.

Data were analyzed using Stata 10 [14].



Cholesteatoma in a 22-year-old male. Permission to use the picture was kindly granted by Björn Åberg, consultant, ear surgeon, Lovisenberg, Diakonale Sykehus, Oslo, Norway.

### RESULTS

From 1 January 1977 to 31 December 2007, a total of 19,158 hospitalisations with STMEC were recorded, i.e. cases which had a cholesteatoma diagnosis combined with a relevant surgical code. From 1 January 1995 to 31 December 2007, a total of 263 outpatient visits with a STMEC were recorded. In total, we identified 19,421 registrations of STMEC distributed among 13,606 different patients, and thus a total of 13,606 cases of STMEC1.

#### Overall incidence rates

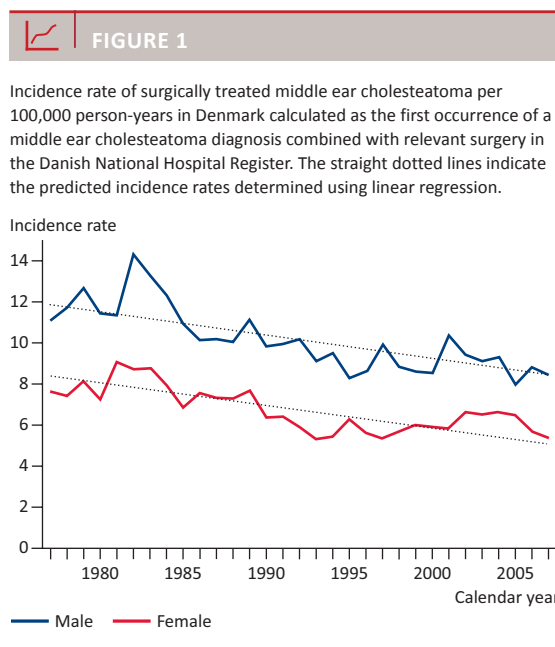
The incidence rate of STMEC1 in Denmark in the period from 1977 to 2007 for males and females is illustrated in **Figure 1**. The male:female ratio for the whole period was 1.51 (95% confidence interval (CI) 1.46-1.56).

The highest male incidence rate was found in 1982 with 14.3 per 100,000 person-years and the corresponding lowest rate was observed in 2005 with 8.0 per 100,000 person-years. For females, the incidence rate peaked in 1981 with 9.1 per 100,000 person-years and the lowest recorded value was seen 1993 with 5.3 per 100,000 person-years.

From 1977 to 2007, we found a statistically significant linear decrease of 0.14 per 100,000 person-years in the annual incidence rate of STMEC1 for males (95% CI 0.10-0.17) and 0.09 per 100,000 person-years for females (95% CI 0.06-0.12)

The most recent incidence rate estimations in our study, i.e. the incidence rates from 2007, revealed an incidence rate of STMEC1 for males of 8.5 and for females of 5.4 per 100,000 person-years.

Data on outpatients before 1995 were not available from the DNHR. However, while STMEC was registered in 7,712 hospitalisations from 1995 to 2007, this was only the case for 263 outpatient visits, equalling 3.3% in



said period. This proportion showed an annual linear increase of 0.38 percent per year (95% CI 0.16-0.60).

#### Age- and gender-specific incidence rates

Figure 2 shows the age-specific STMEC1 incidence rates.

The highest incidence rate recorded was seen at approx. nine years of age for both genders with a maximal annual incidence rate of 21.4 per 100,000 person-years for males and 13.6 for females per 100,000 person-years.

The median age at STMEC1 was 32 years for males (25th percentile, 14; 75th percentile, 51) and 35 years for females (25th percentile, 15; 75th percentile, 54). From 1977 to 2007, we observed a linear decrease in the median age at STMEC1 from 35 years to 28 years for males and from 36 years to 28 years for females.

#### Number of operations per patient

In the period 1977-2007, 13,606 patients had a total of 19,421 STMECs. 70% (n = 9,589) had only one, 21% (n = 2,802) had two; 6% (n = 807) had three; and 3% (n = 408) had four or more STMECs. For patients with two or more STMECs, the median time between two adjacent STMECs was 24 months (25th percentile 12; 75th percentile 52; range 0-350). These numbers include re-operations as well as planned two-step operations, surgery for new cholesteatomas and surgery on contralateral ears, because it was not possible to distinguish these in the DNHR.

#### DISCUSSION

We found a statistically significant decrease in the inci-

dence rate of STMEC1 in Denmark from 1977 to 2007 for both males and females. The highest incidence rates observed – 14.3 for males and 9.1 for females per 100,000 person-years – were recorded in early 1980s, while the incidence rates in 2007 were 8.5 for males and 5.4 for females per 100,000 person-years.

The male:female incidence rate ratio for the period was 1.51.

Both sexes had the highest incidence rate of STMEC1 around the age of nine years. The median age at STMEC1 was 32 years for males and 35 years for females.

The observed decline in the incidence rate of STMEC1 is in accordance with the findings of two Finnish studies. *Alho et al* found a decline in the number of new surgical cases of both cholesteatoma and chronic suppurative otitis media from 1965 to 1992 [5], and *Kempainen et al* observed a statistically significant decline in the incidence rate of cholesteatoma from 1982 to 1991 [6]. In contrast, *Padgham et al* found no change in the incidence rate of cholesteatoma surgery from 1966 to 1986 in a study from Scotland [4].

The cholesteatoma incidence rate in the study period may have been associated with an increasing incidence of grommet insertion and adenoidectomy. These treatments act by eliminating negative middle ear pressure and thus prevent the development of retraction pockets.

Children who required multiple ventilation tube insertions due to persistent or refractory middle ear disease were at increased risk of cholesteatoma in a population-based cohort study by *Spilsbury K. et al*. They observed a reduced rate of cholesteatoma development when the first ventilation tubes were inserted at an early age, when subsequent ventilation tubes were inserted without delay, and when adenoids were removed [16].

During insertion of ventilation tubes, squamous epithelium may be pushed into the middle ear, thus theoretically comprising a risk for the development of an iatrogenic cholesteatoma. In a study by *Al Anazy FH*, the rate of iatrogenic cholesteatoma following ventilation tube insertion was 0.62% when done by residents and 0.33% when performed by consultants [17].

*Padgham et al*, however, found no change in the incidence rate of cholesteatoma, despite a sixty fold increase in the number of inserted ventilation tubes from 1966 to 1986 [4].

Thus, the influence of grommet insertion on changes in the incidence rate of cholesteatoma remains unresolved.

Infection of the middle ear has been proposed as a possible mechanism that causes retraction pockets to develop into cholesteatomas [18]. The majority of the

FIGURE 2

The age-specific incidence rate per 100,000 person-years for surgically treated middle ear cholesteatoma in Denmark, calculated as the first occurrence of a cholesteatoma diagnosis combined with relevant surgery in the Danish National Hospital register. The graph was smoothed using the moving 5-year average.



patients operated for cholesteatoma already had chronic ear disease according to a study by *Alho et al* from the 1940s and 1950s, and the authors suggested that the introduction of antibiotic treatment in the mid-1950s may have been a contributing factor to the observed decline in the incidence of cholesteatoma [5]. Further studies on the association between antibiotic treatment for middle ear disease and the incidence rate of cholesteatoma are needed.

Only few cases of family clustering of acquired cholesteatoma have been published. These cases, however, indicate that hereditary factors interplay with other factors in the pathogenesis of cholesteatoma [19, 20]. Our finding of an increased incidence rate of STMEC1 in the early 1980s and a subsequent decline may also partially be explained by the expanding use of otomicroscopy causing a temporary increase in new cases.

The high male:female incidence rate ratio is in agreement with the observations made in studies by *Kemppainen et al.* and by *Pedersen* demonstrating a male:female ratio of 1.4 [6] and 1.5 [2], respectively.

The high occurrence of STMEC1 around the age of nine years has not been demonstrated in previous studies. *Kemppainen et al* determined that the incidence rates peaked in the third decade for males and in the fourth decade for females. They found that the median age for males was 38 years and for females 45 years [6]. *Alho et al* found that the mean age at cholesteatoma surgery increased from 32 years in 1965 to 42 years in 1992. Part of the reason that our patients were younger may be that we only included the first-time cholesteatoma in any given patient. Earlier diagnosis may also explain part of the observed decline in the median age at STMEC1 in our study.

Patients who were operated before 1977 may incorrectly have been included as new cases of STMEC1 in our study if they received a second operation during our study period. This may have caused a minor overestimation of the incidence rate during the first years of the study period. However, we found that only 30% of the patients underwent more than one cholesteatoma operation in the study period and the median time between two surgical procedures was 24 months. We therefore assume that the impact of this bias diminished within a few years after 1977.

The DNHR only contains data on outpatients from 1995 onwards, and surgery performed on outpatients from 1977 to 1994 was thus not included in our study. However, cholesteatoma surgery performed on outpatients from 1995 to 2007 comprised only 3.3% of the total number of cholesteatoma operations in the period. From 1995 to 2007, this proportion showed a significant increase and we believe this proportion to have been

even more limited in the beginning of the study period. We therefore consider this error negligible.

Cholesteatomas are rarely histologically examined. In most cases, the diagnosis is made by the use of microscopy during surgery. There might have been some discrepancies in the criteria used for making a cholesteatoma diagnosis between surgeons. However, we consider this source of error to be of minor importance.

The diagnostic coding system changed in 1994 and the surgical coding system was modified in 1996 as described in the method section. However, no abrupt changes in the incidence rates were seen at these times.

The present study has several strengths. The DNHR has been carefully validated [7] and the positive predictive value and the degree of completeness of STMEC1 were found to be within an acceptable range, and, moreover, they balanced one another. To our knowledge this is the first study of the STMEC1 incidence rate based on a nationwide register providing a study population of more than five million people and a study period of 31 years.

In summary, a statistically significant decrease in the incidence rate of STMEC1 in Denmark during the past 31 years was demonstrated. The study revealed a male:female ratio of 1.51. In 2007 the incidence rate of STMEC1 was 8.5 per 100,000 person-years for males and 5.4 per 100,000 person-years for females. The age-specific incidence rate peaked around the age of nine years for both genders.

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**CONFLICTS OF INTEREST:** None

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