Nationwide trends in surgery and radioiodine treatment for benign thyroid disease during iodization of salt

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Abstract:

Objective: Iodization of salt was introduced in Denmark in 1998 because of mild-to-moderate iodine deficiency (ID). The aim of this study was to analyze the utilization rate of surgery and radioiodine therapy for benign thyroid disorders before and after the introduction of iodization and to study a possible association between the changes and the raised iodine intake.

Design: A nationwide register study.

Methods: Information on operations and radioiodine treatments for benign thyroid disorders was extracted from nationwide registers in the years 1990 to 2007. Treatment rates are presented for surgery and for radioiodine separately and as a combined rate, both nationwide and split into regions of prior mild and moderate ID.

Results: A total of 65,605 treatments were identified; 26,456 operations and 39,149 radioiodine treatments. In the first years of iodization (1998-2000) (rate-ratio 2000/1997) the combined treatment rate increased with 2.5% (95% confidence interval (CI):−1.8-7.1). Split by prior ID-level the increase was seen in the region of moderate ID, but a decrease in mild ID. After 2000, the combined rate decreased, and ended up being 11.1% (95% CI: 7.1-15.0) lower in 2007 than before iodization (rate-ratio 2007/1997). The changes were primarily due to changes in use of radioiodine therapy as the surgery-rates remained almost constant.

Conclusions: Iodization seemed to be associated with a temporary increase in the utilization rate of surgery and radioiodine therapy in the region of prior moderate ID, probably as a result of treatment of iodine-induced hyperthyroidism, but the rates ended up lower than before iodization.
Introduction

Iodine fortification of salt has been initiated in many countries in the last decades. The latest estimation by WHO shows that about 70% of households throughout the world have access to iodized salt (1). A major argument for increasing the iodine intake by an iodine fortification programme in mildly and moderately iodine-deficient areas is to prevent thyroid growth and autonomy, and thereby goitre and hyperthyroidism (2). A criterion for success of an iodization programme is that fewer persons become patients suffering from iodine deficiency disorders. Using the words of Delange: “…it has to be clearly understood that the ultimate goal of any program of iodine supplementation is to normalize thyroid function at the individual level. It is not only to organize access to iodized salt nor to increase the urinary iodine.” (3). Only few studies in Europe have analyzed in detail the change in the number of patients being treated in a population before and after an iodization program (4). In Denmark there are three main treatment options for an enlarged thyroid gland and/or hyperthyroidism: antithyroid medication, surgery, and radioiodine treatment. While levothyroxine therapy is widely used for non-toxic goitre in some European countries, this treatment is rarely used in Denmark (5). On the other hand, radioiodine therapy is widely used for non-toxic goitre in Denmark (5).

In Denmark iodine fortification was started as a voluntary programme of adding iodine to salt in 1998 (adding 8 p.p.m. iodine to all salt). The fortification was made mandatory in 2000 (adding 13 p.p.m. iodine to household salt and salt used in the commercial production of bread) because of limited use of iodized salt during the voluntary programme. Studies of population groups showed that the prevalence of thyroid enlargement among adults was reduced from 17.6% before iodization to 10.9% after iodization, estimated by ultrasound (6). The incidence of hyperthyroidism also decreased, although after a modest, temporary increase in the early years after iodization (7). A decrease in the incidence of hyperthyroidism and in thyroid size observed by ultrasound is interesting, but to be clinically relevant this should lead to a decrease in the number of patients treated. The incident use of antithyroid medication has been analyzed and the results published in a previous report, showing similar trends as for the studies of the incidence of hyperthyroidism (8). In this study we
focus on the use of surgery and radioiodine treatment and whether iodization of salt affected the frequency of operations and radioiodine treatments for benign thyroid disease in Denmark.

Materials and Methods

Setting

The Danish population comprises around 5,300,000 inhabitants. A unique ten-digit identification number, which is assigned to every person in Denmark at birth or immigration, is used in all contacts with public services including hospitals. The identification number facilitates linkage on an individual level and over time, making the use of registers feasible for evaluation of changes in health care services.

The Danish National Patient Registry keeps records on all hospital admissions in Denmark since 1977 and each hospitalization is classified according to the International Classification of Diseases (ICD) (Until 1994 the ICD-8 and from 1994 the ICD-10 (ICD-9 was never introduced in Denmark)). All operations and most treatments performed are classified according to the National Board of Health’s classification of operations and treatments (3rd version in the period 1989-1995 and 4th version in the period 1996-2007), which are standardized in the Nordic countries. Coding is essential for departments in hospitals as the codes are used in the calculation of productivity, and thereby the financing of the department. The register thus has nationwide coverage and a high validity, especially for surgical procedures (9). Denmark has a tax-financed health care system with free access for all citizens to public hospitals for essential treatments, including operations. The privately financed hospital sector is small, comprising approximately 1 % of hospital beds in 2001 (10).

Identification of operations
All hospital admissions in the period 1990-2007 that included one or more codes for operations (resections, lobectomy or total thyroidectomy) on the thyroid gland were studied (Nordic Classification of Surgical Procedures codes: 08060-08220 before 1996; BAA20-BAA60 after 1996). Procedures coded with more than one operation code (e.g. lobectomy with resection of the other lobe) for the same person, on the same date, counted as one operation only. Operations performed up to three months prior to, or during a hospitalization classified with a diagnosis of thyroid cancer (ICD-codes DC73.9 or 19399), were excluded in order to analyze the trends in the treatment frequency of benign thyroid disorders only. The yearly number of total thyroidectomies because of thyroid cancer was 95 in 1990, 112 in 1997, and 157 in 2007. Furthermore, 97 operations (0.37 %) were excluded because the patients did not have a Danish identification number or because of missing information on place of residency.

Identification of radioiodine treatments

Departments performing radioiodine treatments are required to report to the National Institute of Radiation Protection the number of treatments performed (doses given), the average administered activity, and information whether the treatment is given for benign or malignant disease. This registration did not use the Danish identification number until 2004 when radioiodine treatment was assigned a treatment code in The Danish National Patient Registry. Consequently we were not able to link information on radioiodine treatment on an individual level to other national registers to gain information on residency, sex, and age. Instead, information on the location of the hospital treating the patients was used as proxy for residency of patients. According to national regulations out-patient treatment only includes treatment up to a certain dose of $^{131}$I (600 MBq). Fractioned doses to achieve a higher total dosage are rarely given. Thus, in the present study we considered one dose equivalent to one treatment.

Combined treatment rate
The choice among the two treatment modalities not only depends on clinical features but also on availability and the personal preference of the patient and the physician. There is a known difference among physicians in eastern and western Denmark as regard preferences between surgery and radioactive iodine (11). A combined treatment rate was therefore constructed by simply adding the number of radioiodine doses given and the age-adjusted number of operations performed for each year and geographical region to analyze the total treatment activity before and after iodization.

**Iodine intake**

Iodine intake is lower in the western part of Denmark than in the eastern part, primarily because of a difference in the level of iodine in ground water (12). Prior to fortification, the median urinary iodine excretion in spot urine samples was 45 µg/l (54 µg/l among persons taking a daily iodine-containing supplements) in the city of Aalborg, in the western part of the country, and in Copenhagen, in the eastern part of the country, 61 µg/l (68 µg/l among persons taking daily iodine supplements). Of the investigated persons 34.5% took a daily iodine-containing supplements (13). Thus the two cities were considered respectively moderately and mildly iodine-deficient according to criteria outlined by WHO (1). After fortification, median urinary iodine excretion rose to 86 µg/l in Aalborg and 99µg/l in Copenhagen among persons not taking iodine containing supplements, and 93 µg/l and 108 µg/l, respectively, when including the 29% of the investigated persons taking iodine containing supplements, (14). The iodine intake in Aalborg and Copenhagen represents the geographical difference in iodine intake between the western and the eastern part of Denmark before iodization of salt (15).

**Statistical methods**
For calculations Denmark was divided into two regions, Eastern and Western Denmark, through the Great Belt. Region of residence/treatment was used as a proxy for iodine status. The population comprises about 2,950,000 inhabitants in the western region and about 2,350,000 inhabitants in the eastern region.

Data processing and statistical analyses were performed with SAS 9.2 statistical software (SAS Institute Inc., Cary, NC, USA). To adjust for changes in the mean age of the Danish population, over time, rates were standardized, when possible, to the age composition of the Danish population in year 2000.

The yearly rates were compared with the rate before iodization (1997) by use of Poisson regression to model the association between treatment utilization and calendar year. The level of significance was set to 5%.

The Danish Data Protection Agency approved the present study (No.2007-58-0015). No ethical approval is required for retrospective registry studies in Denmark.

Results

A total of 65,605 treatments for benign thyroid diseases were identified; 26,456 operations and 39,149 treatments of radioiodine (Table 1).

The nationwide, combined treatment rates (surgery + radioiodine) showed an initial increase from 1990 to 1997. From 1997, the year before introduction of the iodization program, to 2000 the rates still increased but with a lower gradient. This increase amounted to a 2.5 % (95% confidence interval (CI):−1.8-7.1) higher rate in 2000 than in 1997. From 2000 the rates declined, however followed by a small increase in 2007, and ended up being 11.1 % (95% CI: 7.1-15.0) lower in 2007 than the rate in 1997. When splitting the combined treatment rates into the two regions the rates were very equal in the early years (1990-1995), after which they started to diverge (Fig. 1b). In the eastern part of the country the treatment rate decreased, and decreased 13.6 % (95% confidence interval (CI): 7.1-19.6)
from 1997 to 2007. In the western part of the country treatment intensity increased with a peak in 2000/2002, followed by a decline. From 1997 to 2002 this temporary increase in the western part of the country amounted to 12.4 % (95% CI: 6.4 -18.6). However, the rate in 2007 ended up being 9.5 % (95% CI: 4.2 -14.5) lower than the rate before the iodization (1997).

The numbers of operations performed, including all types of benign thyroid surgery, were very stable during the 18 years study period (Table 1). When looking at the age adjusted rates (Fig. 2a), however, there was a significant trend for an annual decrease of 0.75% in the rates (95% CI: 0.3 – 1.2). No statistically significant changes were seen in the use of surgery after iodization, when compared to the rate of surgery in 1997. The type of operation performed for benign thyroid disease, however, changed in this study period. The percentage of total thyroidectomies performed for benign thyroid diseases increased from 2.8 % of all operations in 1990, over 4.4 % in 1997, to 22.9 % in 2007. Still, the percentage of operations performed only on one side of the gland (typically in case of a solitary nodule where malignancy cannot be ruled out by biopsy) remained almost the same (Table 1).

Split into regions, the surgery rates were higher in the western part of Denmark than in the eastern part in all 18 years studied (Fig.2b). The rates also seem to vary more in the western part of Denmark than in the eastern part, showing a small temporary increase after the introduction of iodization, even though the variation from the rate in 1997 in most years was not statistically significant. The variation tended to be larger before than after the iodization. A statistically significant trend for an annual decrease was found in the western region (of 1.0 % (95% CI: 0.3 – 1.7)), but not in the eastern region (0.3 % (95% CI: –0.3 – 0.9)).

The nationwide rates for radioiodine treatment have changed much more than for surgery. Use of radioiodine increased throughout the nineties, reaching maximum in 2001, and then followed by a decline (Fig.3a). When splitting the use of radioiodine by region two different patterns emerge (Fig.3b). In the eastern region the use of radioiodine increased until 1994, followed by a small decline in the treatment rate until 1997/98 and larger decline around 2000 and 2002. In the western
region the increase lasted until 2002 and reached a 20% higher rate than in 1997 (95% CI: 12.2 – 28.3), followed by a decline ending up 12.3% lower than in 1997 (95% CI: 5.8 -18.4).

Discussion

In this study, covering 8 years before and 10 years after iodization of salt, we found that the combined rate of radioiodine and surgery for benign thyroid diseases decreased in the period after the introduction of iodization of salt. This occurred after a temporary increase in the area with prior moderate iodine deficiency. The changes were mainly due to changes in the use of radioiodine, as the rates of surgery were more stable.

We have no knowledge of similar nationwide studies assessing changes in radioiodine treatment and surgery during iodine fortification.

The increase in the use of radioiodine from 1990 to 1997, which is transferred to an increase in the combined rates in the same years, makes it plain that the changes in treatment intensity cannot be explained only by iodization and it could be reasonably stated that a causal relationship between the raised iodine intake and the trends in the utilization rates of surgery and radioiodine is not proved by this study. However, this type of studies are needed if the recommendations of WHO to make cost-benefit analyses of introducing iodine fortification programs in developed countries are to be fulfilled. We can only speculate on the increased use of radioiodine treatment in the first part of the nineties, but it could be due to changes in the treatment preferences of the physicians, as radioiodine was introduced as treatment of non-toxic nodular goitre in several European countries, including Denmark (11; 5) It could, however, also be the result of other factors such as higher diagnostic activity of thyroid disease.

It seems that radioiodine was not used as alternative to thyroid operations, as surgery rates were very stable and it may well be that more persons chose to undergo treatment when having a non-surgical treatment option. On the other hand, the temporary increase in the use of radioiodine in the western region in the early years after iodization could be due to iodine-induced hyperthyroidism, as
the incidence of hyperthyroidism increased temporarily after initiation of iodine fortification, especially in the area of moderate iodine deficiency before iodization (7; 8). From this interpretation it follows that the decrease seen in the eastern region may not have occurred, and that the increase seen in the western region in the nineties might have continued, had it not been for the introduction of iodization.

The increase could also be caused by the physicians being more alert to the presence of thyroid disorders and thus by a more liberate use of diagnostic tests. In Denmark there have been a steady increase in the number of tests used in the years studied (7). However, this could only explain the increase in the area of prior moderate ID, not the subsequent decline in that area, nor the steady decline in the eastern area. Indeed, the increase in testing might have led to an underestimation of the “true” decline.

The use of radioiodine following iodization was highly dependent on prior iodine intake with a temporary bulge in treatment only in the moderately iodine-deficient region, probably as a result of treatment of iodine-induced hyperthyroidism. The same pattern was observed in an earlier study on the incident use of antithyroid medication (8). This variation supports the role of iodine as a causal factor behind the variation observed and against that it being only the result of spontaneous variation.

In the present study we analyzed the number of radioiodine doses given, not the number of patients treated. As high dietary iodine intake is associated with a low thyroid radioiodine uptake, it could be speculated, that more patients needed two or more treatments after iodization than before, which would underestimate the decrease, if analyzed as number of patients. On the other hand, radioactive iodine was no longer a treatment option for some patients with non-toxic goitre due to lower iodine uptake and even though most of these patients were probably operated, some patients may have chosen to refrain from treatment altogether. Another potential source for overestimation of the rates of radioiodine treatment is the lack of age-adjustment, as the mean age of the Danish population is known to have increased over time in the study period. If we had left out age-adjustment in the analyses of surgery rates, we would have overestimated the rates in the last 5 years by about 3%.
In contrast to radioiodine, surgery rates were more stable in this period. The type of operation chosen by the surgeons, though, changed towards an increased use of total thyroidectomies for benign thyroid disease during late years. This could have been the result of more difficulties in treating hyperthyroidism with antithyroid medication after iodization, but it is more likely the result of a change of attitude among physicians (16; 17; 18).

Surgery is normally recommended when a patient presents a large or compressive goitre or when malignancy cannot be ruled out, a common situation in the evaluation of thyroid nodules. Two thirds of the operations analyzed in this study were procedures usually performed when facing a solitary nodule, possibly with continued suspicion of malignancy after biopsy (lobectomies or solely unilateral resections). Before iodization, 32% of a general adult Danish population (41-71 yr) were found to have one or more thyroid nodules at ultrasound investigation (19). The increased use of ultrasound examination in the clinical evaluation of patients causes more of these nodules to be detected (20). The percentage of thyroid glands with nodularity have not decreased after iodization in Denmark (6), and it could be speculated that we have to wait for future generations to grow up in an iodine-sufficient environment, without developing thyroid enlargement and nodularity, before we will see a substantial decrease in the rate of surgery. In Sweden, iodine fortification of salt was started in 1936 and augmented in 1966 (21). Thyroid surgery rates in Sweden are 12-36% lower than in Denmark and the rate of radioiodine treatment is almost half of the rate in Denmark (22).

The aim of the Danish iodization program was to increase the iodine intake of the average Dane by 50 µg/day. The median urinary iodine excretion in spot urine samples estimated in the population after the introduction of iodization indicate that the introduction was only sufficient in the eastern region and that the western region remains mildly iodine deficient. To reach the full benefit of the iodization it may be necessary to increase the amount of iodine added.

A pertinent question is how much an enlarged thyroid gland is able to regress. This question has not been fully answered, especially if the tissue has undergone nodular change. Statements vary from limited regression at least in adulthood (23; 24; 25; 26), over widely reversible in young children (25; 27; 28; 29), to widely reversible even late in life (up to 65 yr) (30). In Denmark, the prevalence of
thyroid enlargement in adults decreased after iodization, as mentioned in the introduction. Also the prevalence of large goitres, greater than 50 ml, declined from 1.68 % to 0.89 % (6). Thus it seems that at least in Denmark, goitres, and even large goitres, were widely reversible. A cohort effect cannot be excluded though, since the study represents two cross-sectioned studies and not a follow-up study on the same persons. Furthermore, it may be that the decrease in thyroid size in absolute numbers (ml) was too small to affect the rate of treatment such as surgery and radioactive-iodine.

As for other observational studies there are limitations for this study, and a causal relationship cannot be proven. However, if these changes over time were due merely to changes in treatment policy then one would expect the changes to be similar in West and East Denmark. Moreover, the fact that the same pattern of changes was seen for antithyroid medication supports the association to the increased iodine intake and not just to be the results of changes in the choice between treatment options. A strong limitation is that we were not able to analyze the effect of other important factors for the development of thyroid growth and disease, such as smoking, alcohol intake, use of certain drugs, and other goitrogens in the environment. Furthermore the iodine content in milk is known to have increased in Denmark from 1990 to 2000 (31). These factors may have affected the iodine intake of the population and thus influence, and even mask the effect of the fortification program. Finally, the study could not detect undiagnosed and untreated thyroid dysfunction.

In conclusion, this study showed that iodization seemed to be associated with a decrease in the use of radiiodine treatment, after a small, temporary increase in the area with moderate iodine deficiency before iodine fortification. Even though earlier studies have shown a regression in thyroid size after iodization, this regression in size may be too small to results in a decrease in the use of surgery. Apparently around two thirds of operations were performed because of solitary nodules. As the prevalence of nodules has not decreased after iodization, it may take decades before the positive effects of iodization become evident as regards surgical treatment.

Iodization should still be regarded as a preventive measure to avoid future thyroid enlargement and other iodine deficiency disorders and not as treatment for existing disease; yet it seems that some beneficial effects take less time to emerge.
**Declaration of interest:** The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Table 1. Number and characteristics of operations and radioiodine treatments used for benign thyroid diseases in Denmark from 1990-2007.

<table>
<thead>
<tr>
<th>Year</th>
<th>n</th>
<th>% Lobectomies or solely unilateral resections</th>
<th>Female to male ratio (n_female/n_male)</th>
<th>Mean age of patients (range)</th>
<th>n</th>
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<td>1530</td>
<td>-</td>
<td>5.1 (1281/249)</td>
<td>45.8 (0-85)</td>
<td>1175</td>
</tr>
<tr>
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<td>1455</td>
<td>-</td>
<td>5.1 (1216/239)</td>
<td>45.6 (15-88)</td>
<td>1354</td>
</tr>
<tr>
<td>1992</td>
<td>1503</td>
<td>-</td>
<td>4.7 (1238/265)</td>
<td>46.3 (13-87)</td>
<td>1592</td>
</tr>
<tr>
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<td>1540</td>
<td>-</td>
<td>5.6 (1305/235)</td>
<td>45.5 (13-87)</td>
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<td>1393</td>
<td>-</td>
<td>5.2 (1168/225)</td>
<td>46.0 (12-87)</td>
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</tr>
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<td>-</td>
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<td>45.8 (9-89)</td>
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<tr>
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<td>46.7 (6-91)</td>
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a Initiation of voluntary iodization
b Initiation of mandatory iodization
c 1990-1995: codes do not allow separation of solely unilateral surgery and other procedures.
Legends to figures:

Fig.1. Combined rates of surgery and radioiodine. A: Nationwide combined annual rates. B: Combined annual rates split into region of prior mild or moderate iodine deficiency (ID). The rate in 1997 (The year before introduction of iodization of salt) has been marked by a broken line for easier comparison.* Significant difference between the rate the investigated year and the rate in 1997 (p<0.05).

Fig.2. Surgery. A: □ Nationwide annual rates of all performed operations for benign thyroid diseases, including total thyroidectomies. ■ Annual rates of total thyroidectomies. B: Annual rates of performed operations for benign thyroid diseases split by region of prior mild or moderate iodine deficiency (ID). The rates are adjusted according to the age composition of the population in Denmark in year 2000. The rate in 1997 has been marked by a broken line for easier comparison. * Significant difference between the rate the investigated year and the rate in 1997 (p<0.05).

Fig.3. Radioiodine. A: Nationwide, annual rates of radioiodine treatments for benign thyroid diseases. B: Annual rates of radioiodine treatments for benign thyroid diseases split by region of prior mild or moderate iodine deficiency (ID). The rate in 1997 has been marked by a broken line for easier comparison. * Significant difference between the rate the investigated year and the rate in 1997 (p<0.05).
Fig. 1

A

Treatments per 100,000 person years

Year


B

Treatments per 100,000 person years

Year


Layout:

A

B
Fig. 2

A

B

Layout:

A

B
Fig. 3

A

B

Layout:

A

B