Overdiagnosis of thyroid cancer in the Marne and Ardennes Departments of France from 1975 to 2014

Évaluation du surdiagnostic du cancer de la thyroïde dans les départements de la Marne et des Ardennes de 1975 à 2014

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Abstract

Objectives. – Incidence of thyroid cancer has increased considerably in France in recent years, but the mortality rate has declined only slightly. Part of this increased incidence could be attributable to overdiagnosis. We aimed to estimate the contribution of overdiagnosis to the incidence of papillary thyroid cancer. Material and methods. – Incidence rates were calculated based on data from the specialised Marnes-Ardennes thyroid cancer registry, for cancers diagnosed between 1975 and 2014, by age category and by five-year period. The population was divided into two groups according to pTNM classification at diagnosis (i.e. localised or invasive). Overdiagnosis was defined as the difference in incidence rates between the invasive cancer and localised cancer groups. This rate was then divided by the incidence rate in the localised cancer group for the most recent period (2010–2014) to obtain the proportion of cancers attributable to overdiagnosis. Results. – In total, 2008 patients were included. The proportion of incidence attributable to overdiagnosis for the period 2010–2014 was estimated at 7 and 62% in men and women aged < 50 years respectively, and at 65 and 73% respectively in men and women aged ≥ 50 years. Conclusion. – We observed a high proportion of cancers attributable to overdiagnosis. This finding raises the issue of patient management, with the risk of overtreatment, and the repercussions on quality of life for patients diagnosed with cancer.

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Keywords: Thyroid neoplasms; Thyroid gland; Incidence; Overdiagnosis

Résumé


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1. Introduction

The incidence of thyroid cancer has been increasing for several decades [1,2]. In France, in 1980, the incidence rate per 100,000 inhabitants was 1.0 in men and 2.9 in women [3]. By 2012, this rate had risen to 5.5 in men and 13.8 in women [4]. This increase is mainly driven by an increase in the number of papillary cancers, and particularly, small tumours (< 20 mm) [2,5]. Several authors have proposed possible explanations for this phenomenon [5,6], and progress in diagnostic techniques is regularly cited [7,8]. However, although there has been a substantial increase in the rate of thyroid cancer in France, the mortality rate has only slightly declined, from 0.4 in men and 0.6 in women in 1980, to 0.2 in both men and women in 2012 [4], and the mortality rate has even remained stable in the USA [6].

These circumstances suggest the likelihood that part of this increase in incidence is due to overdiagnosis. Overdiagnosis is defined as the diagnosis of disease that would otherwise not go on to cause symptoms or death [9], and this phenomenon has already been studied in the context of breast and prostate cancer [9,10]. To the best of our knowledge, the impact of overdiagnosis on thyroid cancer incidence has never been studied in France.

Therefore, we aimed to estimate the proportion of the increase in differentiated papillary thyroid cancer incidence that could be attributed to overdiagnosis in the Marne and Ardennes Departments of France between 1975 and 2014 using data from the Marne-Ardennes thyroid cancer registry.

2. Subjects and methods

2.1. Study design

Observational, descriptive, longitudinal, historical cohort study using data from the specialised thyroid cancer registry of the Marne-Ardennes Departments in France.

2.2. Study population

We included all subjects living in the Marne or Ardennes Departments of France and who were diagnosed with papillary thyroid cancer between 1975 and 2014. We excluded patients in whom cancer stage was not determined.

2.3. Variables recorded

We recorded socio-demographic variables, i.e. age at diagnosis and sex. Cancer characteristics were also recorded, namely year of diagnosis, International Classification of Diseases (ICD) 10th revision code [11] associated with the papillary cancer, and the pTNM 2002 status [12]. Patients with cancers classed as ICD codes 8260, 8340, 8341, 8342, 8343, 8344, 8350 were included.

Cancer stage was defined using the pTNM classification at diagnosis, and based on this classification, patients were divided into two groups according to the size of the tumour, the extent of spread beyond the thyroid, lymph node involvement, and presence of metastasis at diagnosis. The “localised cancer” group comprised patients with cancers classified as pT1 or pT2, pN0 or Nx, or M0. The “invasive cancer” group comprised patients with cancer classified as stage pT3 or pT4 and/or pN1 or M1.

2.4. Statistical analysis

Quantitative variables are described as mean ± standard deviation (SD) or median, and qualitative variables as number (percentage).

2.4.1. Incidence rate for papillary thyroid cancers

All calculations of incidence rates were stratified by sex. Incidence rates were calculated per 100,000 person-years (PY), by 5-year age groups (0–4 years, 5–9 years, 10–14 years etc) and by 5-year periods (1975–1979, 1980–1984, 1985–1989, 1990–1994, 1995–1999, 2000–2004, 2005–2009, 2010–2014). The numerator was the number of newly diagnosed cases of papillary cancer, and the denominator was the population of the Marne and Ardennes Departments, by age category and by 5-year period, and by sex (population data from the National Institute of Statistics and Economic Studies, France [13]). The number of person-years was calculated as the sum of the population on 1st January of each of the 5 years (for example, for women for 1975–1979, the number of person-years was the number of women on 1st January 1975 + on 1st January 1976 + on 1st January 1977 + on 1st January 1978 + on 1st January 1979). Direct age standardization was performed using the world population as reference [14,15].

2.4.2. Incidence rate of overdiagnosis

All overdiagnosis analyses were stratified by age and sex. The population was divided into two age groups, namely above and below the median age at diagnosis of the study population.

Overdiagnosis is defined as the diagnosis of disease that would otherwise not go on to cause symptoms or death, and was calculated by comparing the incidence rate of the localised cancer group and that of the invasive cancer group, according to the methodology used in a recent study [16].

In view of the increase in the incidence rate (IR) of thyroid cancer since 1975, the IR for the most recent
period (2010–2014) was compared to that of the first period for which data were available (1975–1979) for each group (IR\textsuperscript{+}\textsubscript{invasive} = IR\textsubscript{2010–2014(invasive)} − IR\textsubscript{1975–1979(invasive)} and IR\textsubscript{+}\textsubscript{localised} = IR\textsubscript{2010–2014(localised)} − IR\textsubscript{1975–1979(localised)}).

We considered IR\textsuperscript{+}\textsubscript{invasive} to represent the true natural course of thyroid cancer. IR attributable to overdiagnosis was calculated by subtracting the increase in the invasive group from the increase in the localised group (IR\textsubscript{overdiagnosis} = IR\textsuperscript{+}\textsubscript{localised} − IR\textsuperscript{+}\textsubscript{invasive}). By dividing this adjusted rate by the IR for the localised cancer group for the most recent period, we obtained a percentage estimating the proportion attributable to overdiagnosis (IR\textsubscript{overdiagnosis}/IR\textsubscript{2010–2014(localised)})\times 100 [16,17].

All analyses were performed using SAS version 8.2 (SAS Institute Inc., Cary, NC, USA).

### 3. Results

In total, 2009 patients were included in this study, but one was subsequently excluded for lack of surgery (tumour size unknown, N0 and M0, thus impossible to classify). Our final analysis included 2008 patients; 1589 (79%) were women; average age was 48 ± 15 years, with a median age of 49 years. The two age groups were thus < 59 and ≥ 50 years.

Overall, 1695 (84%) of patients were stage pT1 or pT2 and 313 (15%) were pT3 and pT4; 437 (22%) were N1, and 40 (2%) were M1. The localised cancer group comprised 1423 patients (71%), and the invasive cancer group comprised 585 (29%).

The changes in age-standardised incidence rates per 100,000 in men and women, by 5-year period, are shown in Fig. 1. The changes in age-standardised incidence rates per 100,000 in localised cancer and invasive cancer, by 5-year period, are shown in Fig. 2. The standardised incidence rate for localised cancer increased by 6.30 cases per 100,000 PY between the 1975–1979 period and the 2010–2014 period. The standardised incidence rate for invasive cancer increased by 1.87 cases per 100,000 PY between the 1975–1979 period and the 2010–2014 period. The increase in incidence in invasive thyroid cancer over time were non significant but it does not decrease. Standardized incidence rates per 100,000 by 5-year period for men and women aged < 50 years are shown in Table 1.

The standardised incidence rate for women aged < 50 years increased by 5.78 cases per 100,000 PY in the localised cancer group, and by 1.58 cases per 100,000 PY in the invasive cancer group between the 1975–1979 period and the 2010–2014 period. The rate attributable to overdiagnosis was estimated at 4.20 cases per 100,000 PY. When divided by the incidence rate of the most recent period (6.75 for the period 2010–2014), the proportion of cases attributable to overdiagnosis was 62% (Table 2).

The standardised incidence rate for men aged < 50 years increased by 0.96 cases per 100,000 PY in the localised cancer group, and by 0.89 cases per 100,000 PY in the invasive cancer group between 1975–1979 and 2010–2014. The rate attributable to overdiagnosis was estimated at 0.07 cases per 100,000 PY. When divided by the incidence rate of the most recent period (1.05 for 2010–2014), the proportion of overdiagnosis was thus 7% (Table 2).

Standardised incidence rates per 100,000 by 5-year period for men and women aged 50 years and over are shown in Table 3.

The standardised incidence rate for women aged ≥ 50 years increased by 4.24 cases per 100,000 PY in the localised cancer group, and by 0.79 cases per 100,000 PY in the invasive cancer
to overdiagnosis was estimated at 1.00 cases per 100,000 PY. When divided by the incidence rate of the most recent period (1.54 for 2010–2014), the proportion of overdiagnosis was thus 65% (Table 2).

4. Discussion

To the best of our knowledge, this is the first study to investigate the proportion of papillary thyroid cancer cases attributable to overdiagnosis in France. The findings are based on registry data, thus ensuring absence of selection bias, and guaranteeing the exhaustiveness of the data across two French Departments over a long period (40 years). Our study shows that there is a substantial proportion of overdiagnosis of papillary thyroid cancer among women aged > 50 years (73%) and < 50 years (62%) as well as in men (73%), in women aged < 50 years (62%) as well as in men aged over 50 (65%). The rate of overdiagnosis was much lower in men younger than 50 years of age, at only 7%.

The changes in incidence rates for papillary thyroid cancer in this study are in line with previous reports in the literature [1,2]. Our findings are similar to those of the study by O’Grady et al. in 2015 in the USA [16]. After age-standardisation on the American population, the proportion of thyroid cancers attributable to overdiagnosis was 45.5% in women aged < 50 years, 60% in women over 50, and 41% in men aged 50 years and over. As in our study, the proportion of overdiagnosis was also much lower in men aged < 50 years, at only 5.5%. However, comparison of these two studies presents certain limits, in that they were not age-standardised on the same population. In addition, O’Grady’s study excluded patients aged under 20, and their classification was somewhat different to ours (i.e. localised cancers measuring more than 4 cm were included in the localised group in O’Grady’s study, whereas they were classed in the invasive group in our study).

We chose not to divide our population into two groups based on TNM staging. Indeed, localised tumours measuring more than 4 cm (and diagnosed clinically by palpation), as well as tumours extending beyond the thyroid capsule, or N1, were not included in the “localised cancer” group in our study. These types of tumours were not considered as attributable to overdiagnosis.

There are several possible explanations for the increase in overdiagnosis [18]. The most likely contributing factors are the advent of echography around 1985, and the progress made in diagnostic techniques (cytology under echographic guidance, hormonal measurements) [19]. In addition, pathology slices of thyroidectomy specimens are ever thinner, leading to diagnosis of very small cancers (at the scale of a millimetre) that had gone undiagnosed before a surgery performed for benign indications (such as goitre or hyperthyroidism). The frequency of millimetre-sized thyroid cancers is estimated at around 36% in the general population [20], thus providing a large reservoir of latent disease.

In our study, the difference in incidence rates attributable to overdiagnosis between men and women aged below 50 years was quite substantial, with proportions of 0.07 and 4.19 per 100,000 respectively. The female/male ratio was high (sex ratio 3.8).

Table 1
Standardised incidence rates per 100,000 persons for papillary thyroid cancer in women and men aged less than 50 years.

<table>
<thead>
<tr>
<th>5-year period</th>
<th>Women &lt; 50 years</th>
<th>Men &lt; 50 years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Localised cancer</td>
<td>Invasive cancer</td>
</tr>
<tr>
<td>1975–1979</td>
<td>0.97</td>
<td>0.59</td>
</tr>
<tr>
<td>1980–1984</td>
<td>1.85</td>
<td>0.75</td>
</tr>
<tr>
<td>1985–1989</td>
<td>1.83</td>
<td>1.24</td>
</tr>
<tr>
<td>1990–1994</td>
<td>2.71</td>
<td>1.41</td>
</tr>
<tr>
<td>1995–1999</td>
<td>3.63</td>
<td>1.61</td>
</tr>
<tr>
<td>2000–2004</td>
<td>3.80</td>
<td>2.25</td>
</tr>
<tr>
<td>2005–2009</td>
<td>4.01</td>
<td>1.89</td>
</tr>
<tr>
<td>2010–2014</td>
<td>6.75</td>
<td>2.17</td>
</tr>
</tbody>
</table>

Table 2
Proportion of incidence attributable to overdiagnosis for the period 2010–2014 in women and men, by age group.

<table>
<thead>
<tr>
<th></th>
<th>2010–2014</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women &lt; 50 years</td>
<td>4.20</td>
</tr>
<tr>
<td>Overdiagnosis rate (per 100,000)</td>
<td>62</td>
</tr>
<tr>
<td>Percentage overdiagnosis (%)</td>
<td>3.45</td>
</tr>
<tr>
<td>Women ≥ 50 years</td>
<td>73</td>
</tr>
<tr>
<td>Overdiagnosis rate (per 100,000)</td>
<td>7</td>
</tr>
<tr>
<td>Percentage overdiagnosis (%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Men &lt; 50 years</td>
<td>41</td>
</tr>
<tr>
<td>Overdiagnosis rate (per 100,000)</td>
<td>65</td>
</tr>
<tr>
<td>Percentage overdiagnosis (%)</td>
<td></td>
</tr>
</tbody>
</table>
Indeed, thyroid disorders, and particularly thyroid cancer, are more frequent in women than in men, with a sex ratio in France ranging from 3.4 to 4.3 [2]. Women also have more frequent medical check-ups (for pregnancy, for example [21] or prescription of oral contraceptives in women aged < 50). The average age of our study population was 48 years, with a median of 49 years, a finding similar to that of other studies from the USA [16], and Australia [22]. It is also established that consumption of healthcare resources increases with age [23], which could explain the difference in the proportion of cases attributable to overdiagnosis between men younger than vs older than 50 years.

While the Tchernobyl accident of 1986 did not have any direct consequences on the level of irradiation in France, it did lead to heightened awareness of thyroid disease among the general population and physicians [24,25].

Among the thyroid cancer cases diagnosed, many would never have progressed and can thus be considered as overdiagnosis. Others were diagnosed when the cancer was localized, corresponding to early-stage disease. The repercussions on incidence rates of these early-stage diagnoses should lead to a subsequent rise in localised cancers, and a reduction in invasive disease. However, we did not observe any such decrease in our study, thus supporting our hypothesis of overdiagnosis.

The risk inherent to overdiagnosis is that patients will be overtreated [9]. Some authors advocate active surveillance or conservative management for very small sized cancers and this approach is currently being investigated [26].

The small number of cases may lead to less precise estimation in incidence rates. A larger study at a national level is warranted to confirm our findings. Nonetheless, this is the first study to date performed on data from France, and the only study to be age-standardised on the world population. This should allow comparison with other studies.

In conclusion, the observed increase in papillary thyroid cancer incidence rates is largely attributable to overdiagnosis. As for other organs, notably the prostate, the prerequisites for thyroid cancer overdiagnosis to occur are a large reservoir of latent disease, and increased diagnostic activity. The consequences of overdiagnosis include overtreatment, which not only generates additional healthcare expenditure, but also has an impact on patients’ quality of life when they are diagnosed with cancer. While we cannot ignore these diagnoses, it is important to recognize potential overdiagnosis and avoid overtreatment, by adhering to recommendations for management issued by professional societies.

Disclosure of interest

The authors declare that they have no competing interest.

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