Decline in breast cancer incidence in the Flemish region of Belgium after a decline in hormonal replacement therapy

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Background: Breast cancer incidence rate in Belgian women was as high as 152.7 for 100 000 in 2003 (adjusted on European population). We made an estimation of the contribution of hormone replacement therapy (HRT) on breast cancer incidence from 1999 to 2005 in women aged 50–69 years in Flanders.

Methods: Breast cancer data were extracted from the Belgium Cancer Registry. Drug consumption was computed from drug sales data. The fraction of breast cancers attributable to HRT was calculated by year, using the relative risks of the Million Women Study in the UK.

Results: The proportion of women aged 50–69 years using HRT in Flanders increased since 1992, peaked at 20% in 2001, then decreased to 8% in 2008. The incidence of breast cancer in 100 000 women aged 50–69 years in Flanders increased from 332.8 in 1999 to 407.9 in 2003, then decreased to 366.1 in 2005; the variations were mostly noticeable for tumors <20 mm in size. The fraction of breast cancers attributed to HRT peaked at 11% in 2001 and decreased afterward.

Conclusion: The high level of breast cancer observed in the years 2001–2003 in Flanders can be partly attributed to the use of HRT. Since participation to mammography screening of Flemish women aged 50–69 years was still on the rise in 2003 and never exceeds 62%, the decrease in breast cancer incidence was likely to be due to the decrease in HRT use and not to screening saturation.

Key words: attributable fraction, Belgium, breast cancer, hormone replacement therapy

introduction

The randomized trial ‘Women Health Initiative Survey’ (WHI) and the prospective ‘One Million Women Study’ (MWS) cohort showed an increased risk of breast cancer in women taking hormone replacement therapy (HRT), principally opposed estrogens [1–3]. These results contributed to the classification of HRT as carcinogenic to humans (i.e. group 1 carcinogens) by the International Agency for Research on Cancer [4].

Cancer incidence data in Belgium are collected and published by the Belgian Cancer Registry (www.belgiancancerregistry.be). Full registration coverage of the country exists since 2004. The Flemish region comprises 60% of the Belgian population, and in this region, complete registration of new cancer cases is available from 1999 until 2005. Flemish cancer incidence data were published in Cancer Incidence in Five Continents of the International Agency for Research on Cancer, Lyon, France [5].

After the year 2000, the breast cancer incidence in Belgium was the highest in Europe [6] and one of the highest in the world [7] with a European age-standardized incidence rate of 152.7 for 100 000 women. The Belgian Cancer Registry uses the Identification Number of the Social Security as unequivocal unique patient identifier, and investigations have shown that this high incidence was not due to some administrative fallacy. One of the possible reasons for this high incidence was the high level of menopausal HRT use by Belgian women. A first report estimated that in 2001, 15% of Belgian women ‡40 years of age took HRT on a regular basis [8], and 75% of use was concentrated in women aged 50–69 years. After 2001, a sharp decrease in the number of women taking HRT occurred. This first report examined changes in breast cancer incidence in one Belgian province (Limburg) comprising only 8% of the Belgian population.

In this article, trends in breast cancer incidence in women aged 50–69 years with breakdown by cancer size are examined for the whole Flemish region of Belgium. A quantitative estimate of the contribution of changes in HRT use on these trends is presented.
methods

breast cancer incidence

The breast cancer incidence data (ICD10 code C50) in Flanders were extracted from the Belgian Cancer Registry from 1999 until 2005. Annual incidence rates are calculated for 100 000 women and adjusted on age distribution of the European population, resulting in European Standardized rates (ESR). Linear regressions were fitted after logarithmic transformation of rates. From slopes, the annual percent changes (APCs) were derived.

The Registry also collects data on pathological and clinical cancer size [T component of the TNM (tumor–node–metastasis) classification]. Pathological sizes were available in 73% of the cases. Using the same statistical methods, the slopes of incidence by pathological size were computed, after a proportional reallocation of missing cases into the classes T1–T4 each year.

use of HRT in Belgium within the age group 50–69 years

Information on drug sales at the national level was obtained from the International Medical Services (IMS). Details on sales of orally or transdermal HRT were available from 1992 to 2006, including the combinations of estrogen and progestin (in one vehicle or separately), estrogen only, and tibolone [10]. Estriol was excluded because it had no impact on breast cancer [11]. A ‘yearly dose’ of HRT is the amount of HRT medication one woman needs for 1-year therapy; it consists of 365 defined daily doses. The number of yearly doses sold in 1 year estimates the average number of women receiving HRT in that year, assuming uninterrupted HRT use during the year. As reimbursement was better for separate selling of progestins and estrogens, for knowing the total amount of women who were taking a combination of estrogen and progestin, we had to calculate the amount of estrogen sold together with progestin. The latter was calculated by assuming that the fall in sales of progestin between 2001 and 2006 was largely due to the reduction in sales of progestin that opposes estrogen.

Secondly, to estimate the HRT use in the Flemish region only from the IMS data, we used regional data on regional repartition of the reimbursed drugs obtained from the ‘Instituut voor Farmaco-Epidemiologie van België’ [12].

Thirdly, for estimating the proportion of women aged 50–69 years among women using HRT, information from the ‘Intermutualistisch Agentschap’ (IMA) was used. The IMA collects data of all Belgian health insurance companies (www.nic-ima.be), and in a random sample of 2.5% of the Belgian population, full details on individual reimbursed medications are registered. Women aged 50–69 years represented 75% of all the women taking HRT [8]. Therefore, the prevalence of HRT use among Flemish women aged 50–69 years in a given year was estimated by multiplying the total estimated number of women taking HRT during that year by 0.75.

calculation of the attributable fraction

Using the formula proposed by Levin [13], we calculated the fraction of breast cancer among women aged 50–69 years attributable to HRT use:

\[
AF = \frac{P(RR-1)}{1 + P(RR-1)}
\]

where \( P \) is the prevalence (%) of the risk factor in the population and \( RR \) is the relative risk associated with the risk factor. The attributable fraction is expressed as a proportion of the risk factor due to the risk factor.

Lag times of 0 (i.e. indicating immediate effect), 1, and 2 years between HRT cessation and subsequent decrease in cancer incidence were used. Best fit between changes in HRT use and changes in cancer incidence was obtained with a 2-year lag time.

Relative risks of breast cancer associated with use of the various types of HRT from the MWS were used [3], that is 1.3 for estrogens, 2.0 for combined estrogens plus progestin, and 1.4 for tibolone. We did not use different relative risks for the different HRT formulations as the MWS did not report significant differences in risk between the different types of estrogens and progestin or combinations of them.

results

incidence

Breast cancer incidence increased regularly in women aged 50–69 years from 1999 to 2003 (APC = 5.4%), after which a sharp decline was observed (APC = −5.3% year) (Figure 1A).

In women younger than 50 years, rates remained unchanged, whereas in women older than 69 years, rates steadily increased by 1.6% per year. In women aged 50–69 years, the most important variations took place in cancer <20 mm in size (Figure 1B), for which the APC was 7.1% from 1999 to 2003 and −5.7% from 2003 to 2005.

HRT consumption

At the national level, main decreases concerned the estrogen–progestin combinations (Figure 2). Estrogen alone also decreased while tibolone continued to increase until 2003.
and then stabilized. The proportion of Flemish women aged 50–69 years, to whom HRT was regularly sold, increased from 1992 until 2001, where it peaked at 20.1% (Table 1), which is 2 years before the peak in breast cancer incidence. Since 2002, it suddenly decreased to reach a level <8% in 2008.

attributable fraction and excess of breast cancers
A lag time of 2 years between HRT use and breast cancer incidence best described the changes in incidence according to changes in HRT use. This 2-year lag time also corresponds to the delay between the year of peak HRT use (2001) and the peak of breast cancer incidence (Figure 4) in women aged 50–69 years (2003). In women aged 50–69 years, the proportion of breast cancer attributable to HRT use 2 years before increased regularly and peaked at 11.1% in 2003 and then decreased (Table 1). The excess of breast cancers that could be attributed to HRT in women aged 50–69 years in Flanders was 200 in 1999, 317 in 2003, and again 203 in 2005.

discussion
Two distinct patterns in recent breast cancer trends are observed in the Flemish region of Belgium in women aged 50–69 years. The incidence rose rapidly in a first phase until 2003 and then decreased slightly from 2003 to 2005.

Sharp increasing trends of breast cancer have been described through the second half of the last century in industrialized countries [14]. They are related to changes in reproductive risk factor profile such as reduced fertility rates or older age at first pregnancy and increasing of obesity. Recently, two new factors susceptible to influence the breast cancer incidence occurred: the implementation of mammography screening and the use of HRT, both of which concern the women of the same age group, 50–69 years old. The mammography screening, by detecting prevalent cases of breast cancers in the first years of the implementation of a program, results in an apparent increase in breast cancer incidence. The use of HRT has been shown to increase the breast cancer incidence [1, 3] and more particularly the incidence of small and nonaggressive tumors [15, 16].

Both mammography screening and HRT use varied strongly over the period of our study. Opportunistic mammography screening started in Flanders at the end of the 1980s; some organized screening projects developed in the 1990s but remained small-scale local initiatives. A national organized mammography screening program was set up in 2001 and coexists with some rate of opportunistic screening.

The use of HRT in Flanders increased strongly from 1992 to 2001. The sharp decrease in HRT use after 2001 was the consequence of the publication of the WHI and of the MWS.

Table 1. HRT use (1996 to 2008), attributable fraction, and number of breast cancer (1999 to 2005) in women aged 50–69 years in Flanders

<table>
<thead>
<tr>
<th>Year</th>
<th>% Women on HRT</th>
<th>Fraction of BC attributable to HRT (%)</th>
<th>Excess of BC attributable to HRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>1996</td>
<td>15.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1997</td>
<td>17.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1998</td>
<td>17.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1999</td>
<td>19.1</td>
<td>9.0</td>
<td>202</td>
</tr>
<tr>
<td>2000</td>
<td>19.7</td>
<td>9.7</td>
<td>233</td>
</tr>
<tr>
<td>2001</td>
<td>20.1</td>
<td>10.5</td>
<td>281</td>
</tr>
<tr>
<td>2002</td>
<td>18.8</td>
<td>10.9</td>
<td>300</td>
</tr>
<tr>
<td>2003</td>
<td>14.2</td>
<td>11.1</td>
<td>317</td>
</tr>
<tr>
<td>2004</td>
<td>11.0</td>
<td>10.5</td>
<td>271</td>
</tr>
<tr>
<td>2005</td>
<td>9.7</td>
<td>7.8</td>
<td>203</td>
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<tr>
<td>2006</td>
<td>8.6</td>
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<tr>
<td>2007</td>
<td>8.1</td>
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<tr>
<td>2008</td>
<td>7.7</td>
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</tbody>
</table>

Breast cancer data were only available for the years 1999 to 2005. HRT, hormone replacement therapy; BC, breast cancer.
We believe that the first rise in breast cancer incidence in women aged 50–69 years reflects the cumulated impact of several factors, such as changes in reproductive risk factors profile over time, the implementation of mammography screening, and the growing use of HRT. The subsequent drop in breast cancer incidence observed after 2003 in women aged 50–69 years follows the reduction in HRT use that started after 2001 and is most probably the consequence of this reduction: indeed, the strong reduction of HRT use is the only environmental change that can explain the decreasing trend in breast cancer incidence in women aged 50–69 years.

Moreover, the two-phases pattern observed in the age group 50–69 contrasts with the quite stable incidence in women 40–49 years old and with the steady increasing incidence in older women. Saturation of mammography screening has been evoked as a possible reason for the decrease in breast cancer incidence observed after 2000, first in the United States and later in several other countries [Geneva (Switzerland), Germany, Norway, UK] [17–19]. ‘Saturation’ refers to the decrease in screen-detected prevalent breast cancer cases because, after several years of screening activities, most women attending screening have incident screens, whereas prevalent screens are confined to women reaching the age for screening [20]. After 2003, rates of mammography screening in Flanders continue to increase and remain moderate: the global rate of mammography coverage (organized and opportunistic together) in the women aged 50–69 years was 33% in 2000, 50% in 2002, 56% in 2004, and 62% in 2006 (Figure 3) [21]. This moderate screening coverage in Flanders during the studied period implies that many women still had an initial (prevalent) mammography after 2003, and thus, screening saturation cannot explain the decrease in incidence after 2003.

We analyzed our data by tumor size (pT). The variations were mostly seen in the small-size tumors (pT1). The strong increase of small-size tumors in the first phase is consistent with the effect of increasing screening coverage as well as the growing use of HRT since both factors increase the incidence of small-size tumors. The subsequent decrease in small-size tumor incidence is less pronounced, indicating competing effects between the mammography screening still on the rise and the reduced use of HRT. A limitation in the interpretation of the variations in tumor size is the rate of missing size (pT). The missing pTs were reallocated on a proportional way based on the assumption that there was no bias in the distribution of missing values. This assumption is plausible since the great majority of breast cancers are operated, so the missing sizes should not be biased in favor of one particular size, but we have no means to verify this assumption.

The number of yearly doses of HRT is derived from the packages sold. We presented this number of yearly doses as an estimate of the number of women who took HRT. In fact, the number of yearly doses underestimates the number of women taking HRT since some women have taken HRT during periods shorter than 12 months. Our figures are thus an underestimation of the women who actually took HRT. Consequently, attributable fractions and the excess in the number of breast cancers due to HRT are also underestimated, and our results are conservative.

We observed a 2-year lag between the start of the reduction of HRT consumption and the decrease in breast cancer incidence (Figure 4), which was slightly more than what was described in the United States [22], but in concordance with the delay observed in Germany [18]. The 2-year lag time is in line with the short-term persistence of carcinogenic effects of HRT after cessation of their use. Probably, this lag time could have been shorter and the fall in incidence could have been stronger if there has not been a concomitant rise in the attendance to mammography screening.

The main limitation of the study is the ecological design as data were not collected on an individual basis. This design does not allow to take into consideration the duration of use of HRT. Another limitation is the short time of the observation period after the reduction of HRT. Of course, the trend has to
be monitored when new data will be available to exclude a transient variation. However, results are consistent with the well-documented relationships existing between HRT use and breast cancer occurrence.

In conclusion, the high prevalence of HRT use in Flanders can explain a part of the high breast cancer incidence in Belgium during the early 2000th past years. This part could have been as high as 11.3% in the year 2003. A drop in incidence of breast cancer in women aged 50–69 years followed the drop in HRT consumption and is likely the consequence of it.

disclosure

The authors claim no conflict of interest.

references

12. IFEB. Register Sales of Reimbursed Drugs per Province. 2009; http://www.ifeb.be (July 2009, date last accessed).