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Changes by age in breast cancer incidence, mammography screening and hormone therapy use in France from 2000 to 2006

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Abstract. **Background.** In 2003, US breast cancer incidence rates fell. Recent French data reveal also a decline in 2005-2006. This study aims to present the trends in breast cancer incidence by age and to identify the respective impact of mammography screening and use of hormone replacement therapy (HRT) in the French context. **Methods.** Breast cancer incidence rates were calculated from the new cases of breast cancer among affiliates of the general scheme of the French National Health Fund between 2000 and 2006. Data concerning HRT and mammograms were extracted from the reimbursement databanks of the National Health Fund and from the National Screening Programme. **Results.** Breast cancer incidence decreased between 2003 and 2006 only for women aged 50 or above. The strongest declines were observed among the 55-59 and 60-64-year-old groups (12.9 and 7.7%, respectively). We observed a slight decline in the age groups of 50-54 and 65-69 (0.7 and 2.1%, respectively). Volumes of mammograms increased continuously between 2000 and 2006 from 1,600,000 to 3,470,000 for women aged 50-74 years old. In 2004, the National Screening Programme achieved complete geographic coverage. At the same time, the number of HRT users has dropped by 62% between 2001 and 2006. We observed the highest prevalence of HRT and the highest decrease in breast cancer incidence rates in the age group of 55-59. **Conclusions.** The recent reduction in breast cancer incidence in France for women aged 50 years or above, in 2005-2006, was accompanied by a substantial reduction in HRT prescriptions after 2002 for all age groups. The drop in HRT parallels the drop in breast cancer incidence for the women between the ages of 55-59 and 60-64. The high-level of development of screening in France during the same period could not account for the reduction in breast cancer incidence. ▲

Key words: breast cancer, incidence, hormone replacement therapy, screening, France

Introduction

Breast cancer incidence rate has continuously risen in France, during the period 1978-2000, by 2.4% per year [1]. The greatest increase was observed in women aged 50-74, with an increase of almost 3% per year between 1983 and 2002 [2]. Recently, we reported a first decline of breast cancer incidence in France, in 2005 and 2006, among women aged 50 years or above [3], like in the United States in 2003 [4], in Australia [5] and in Europe [6]. Possible explanations for these patterns include change in lifestyles, the effects of widespread screening and decreased use of hormone replacement therapy (HRT). The potential contribution of mammography screening and HRT use to those breast cancer incidence trends is unclear, because of marked changes concerning these two factors at the same period in France.

The development of screening was gradual between 1980 and 2004. In 2004, the National Programme achieved complete geographic coverage and targeted eight millions women aged 50-74. This program invites all women for a free mammography every two years with double reading. Between 2000 and 2006, the use of screening mammography has continuously increased, mixing opportunistic and organized screening. Before 2002, the prevalence of HRT use was high. After the publication of the Women's Health Initiative

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(WHI) study [7], use of HRT substantially dropped in France. HRT has been implicated as a risk factor for breast cancer, and the recent decline in breast cancer incidence in the US was largely attributed to the decline in HRT use [4, 8-10]. We have the opportunity to examine by 5-year age groups the incidence trends in France between 2000 and 2006 and the potential association between mammography screening, HRT use and recent changes in breast cancer incidence.

Methods

Our study population comprised female affiliates of the general scheme of the French National Health fund between January 1st 2000 to December 31 2006. The fund includes 86% of the French population. The data cover the entire French territory (28 million women). Breast cancer incidence rates were calculated from the new cases of breast cancer among affiliates of the general scheme of the French National Health Fund who received first time approval for their long-term disorder. In France, their referring physician notified patients with a long-term disease, including breast cancer, to the National Health Insurance. The definition of long-term disorder is not only of a medical nature, but also administrative: those patients are free of co-payments. Annual breast cancer incidence rates were calculated every six months, in January and June (rolling year-to-date values) over the 2000-2006 period for each age group. Population data were retrieved from the National Institute for Statistics and Economics Studies (Insee) datasets. Annual breast cancer incidence rates were age standardized for all age groups with the 2000 French standard population. The data included invasive and *in situ* breast cancer cases (ductal carcinoma *in situ*), but the pathology reports are not recorded, and information on receptor status is not available.

Trends in breast cancer incidence were analysed for women aged 30 to 49, 50 to 69, 70 to74 and over 75 years old. For the group aged 50 to 69, we further investigated incidence rates by 5-year subgroups (50-54; 55-59; 60-64; 65-69). For each 5-year age group, we compared trends in incidence rates between 2003 and 2006. For the broader group aged 50 to 69 years, we calculated relative age-adjusted incidence rates using the Mantel-Haenszel method.

Mammography data were extracted from the reimbursements databanks of the National Health fund for all mammograms performed between 2000 and 2006. The National Institute of Public Health (INVS) collected data of the National Screening Programme. An annual report has been published for evaluation of the screening programme since 1998.

HRT data were extracted from the reimbursements databanks of the National Health fund. Prescriptions defined as HRT were oral or transdermal, estrogen only HRT or combined estrogen-progestagen HRT preparations. Our data based on dispensation do not distinguish between data on estrogen-only HRT and data on combined HRT preparations. We defined users of HRT as anyone who has received at least two HRT prescriptions during the year. HRT data were collected from 2000 to 2007.

Results

In our data, incidence rates increased gradually from mid-1999 to 2006 for women less than 50 years old. Starting in 2004, breast cancer incidence decreased in all age groups among women aged 50 years or above, although the magnitude and timing of decrease varied by age *(figure 1)*. Among women aged 50-69, the decrease began in mid-2003, and between 2003 and 2006 the percentage decrease was 6.3 (95% CI: 4.6 to 7.9%). For women of 70-74 years old, the incidence increased by 25% (95% CI: 20.2 to 30.0%) from 2002 to 2004, after the implementation in 2002 of organized screening in this age group, and decreased 8.4% (95% CI: 4.9 to 11.9%) from 2004 to 2006. In the group of women of 75 years old and above, the incidence decrease was 3.7% (95% CI: 0.6 to 6.7%) between mid-2004 and 2006.

Figure 2 shows trends in age-specific breast cancer incidence rates in four different age groups among women of 50 to 69 years old. The highest incidence rates were observed in the 60-64 age group between 2000 and 2006. The largest percentage decreases from 2003 to 2006 occurred in women aged 55-59 years old (12.9%; [95% CI: 10.0 to 15.8%]) and 60-64 years of age (7.7%; [95% CI: 4.3 to 10.9%]). For women of 65-69 and 50-54 years old, the decreases were 2.1% (95% CI: –1.6 to 5.8%) and 0.7% (95% CI: –2.8 to 4.1%), respectively.

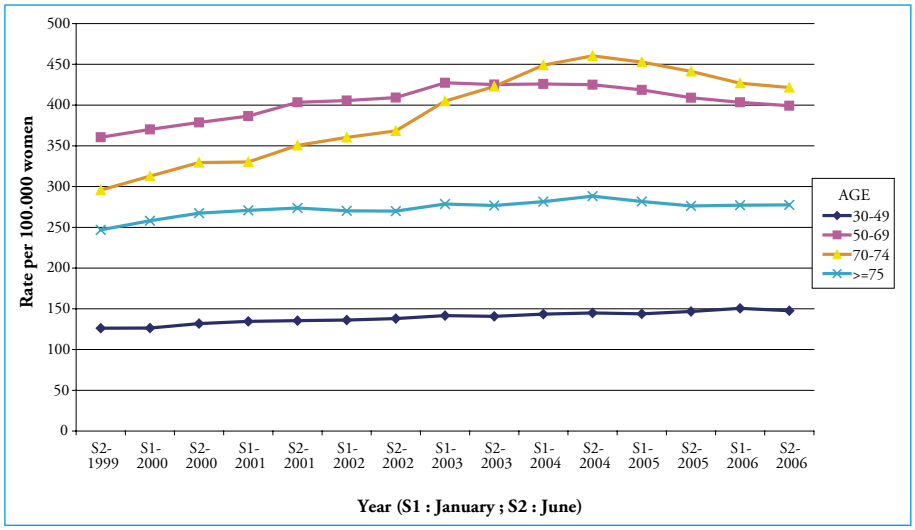

Figure 1. Breast cancer incidence by age.

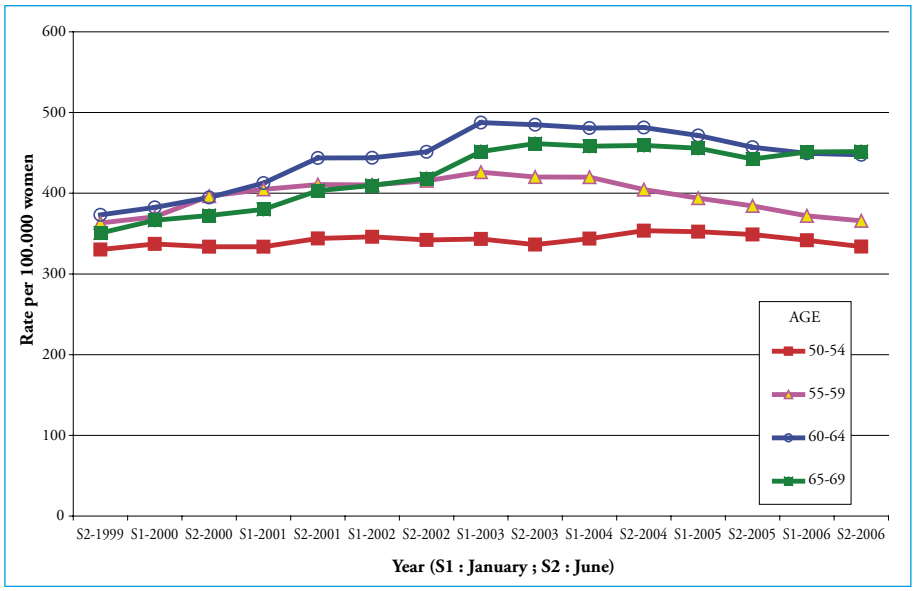

Figure 2. Breast cancer incidence in four age groups.

Data from organized screening showed a rapid increase between 2000 and 2006: 478,450 mammograms in 2000 and 2,080,000 in 2006. Attendance rates increased from 40% in 2004 to 48% in 2006. The use of mammography including opportunistic screening and diagnostic mammography has continuously increased between 2000 and 2006 and all mammograms have increased from 1,600,000 to 3,470,000 for women aged 50-74. 37.3% of this population had undergone a mammography in the last two years in 2001 *versus* 62.8% in 2006. This upward trend concerned all age groups over 50.

Data from HRT use of the National Health Fund showed a decline of 62% from 2001 to 2006 for women aged 50 to 64 years old, with a sharp decrease between 2002 and 2004 in all 5-year age groups *(figure 3)*. HRT use was very common in France for women aged 50-64 years old before 2002 but after 2005, less than 15% of women were receiving this type of treatment. The largest decline occurred in

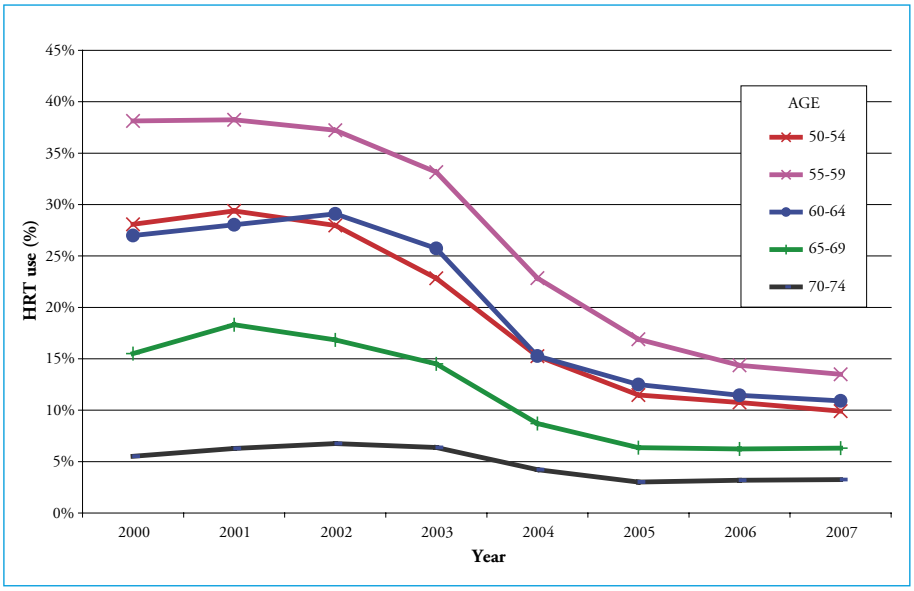

Figure 3. HRT use in five age groups 2000-2007.

women aged 55 to 59 years old: 38.2% were users in 2001, and only 14.5% in 2006.

Discussion

In France, data from cancer registries show that invasive breast cancer incidence has been increasing continuously by an average of about 2.4% per year between 1980 and 2003. Registries are the standard in recording cancer cases, but those registries cover only about 16% of the French population. In this report, we provide national data of the medico-administrative database for long-term disorders between 2000 and 2006. In contrast, our results show a decline in the incidence of breast cancer among women aged over or equal 50 years between 2003 and 2006. Incidence rates include *in situ* and invasive breast cancer cases. Those data are not collected for epidemiological purposes but allow to quickly identifying changes of trends in cancer incidence at the national level. All the women treated for breast cancer are registered, and the system was unchanged between 2000 and 2006.

The magnitude and timing of decrease varied by age, and the highest decline was observed among the women aged 55-59 and 60-64 years old (12.9 and 7.7%, respectively). The decline began mid-2003 and was regular until 2006. In the youngest group (50-54), the incidence rates were almost stable (–0.3%) between 2003 and 2006, and we observed only a slight decrease among the women aged 65-69 (2.1%). Specific data on *in situ* carcinoma are not available in the database. Among the cancers detected by organized screening, the percentage of ductal carcinoma *in situ* was stable between 13 and 15% from 2000 to 2005 [11]. A decrease of *in situ* breast carcinoma has not been documented in France during this period. Somewhat unexpected is the decrease in incidence in 2005 and 2006 after full national coverage of the screening program in 2004. This context is different from the US where the percentage of women that have undergone a mammography in the last two years has stabilized since 1999 [12, 13].

Given these findings, changes in screening are not a major factor contributing to the decline of breast cancer incidence in France. As in other countries (US, Australia, Germany, New Zealand) [4-6, 14], the decrease in breast cancer incidence after 2004 seems to be temporally related to the substantial drop in the use of HRT ensuing the first report of WHI in 2002. Use of HRT was very common in France after 1990 and culminated in 2001. The number of HRT prescriptions dropped by 62% between 2002 and 2006 with a sharp decline in 2004 and 2005. During the same period, a significant fall in breast cancer incidence occurred among women over 50 years. Results from WHI study and from the Million Women Study (MWS) [15] showed a significant increase of breast cancer with increasing total

duration of use in current users of HRT. The observed decrease in HRT use in France was largest in women 55 to 64 years old because in that population HRT use was widespread, and the duration of use was longer. In the 50-54 year age group, incidence rates remained quite stable over this period, and the total duration of use of HRT was lower than five years for the majority of women. In the French E3N cohort study [16], the mean age at treatment was 52.4 years, and 70% of women had used HRT for a mean duration of seven years. Between 50 and 64 years, effects of screening on incidence have been largely obscured by changes in HRT use. The role of HRT may be seen as a promoter fuelling the growth of subclinical hormone-sensitive tumors [17, 18] and increasing breast cancer incidence. On the other hand, HRT is also associated with an increase in mammographic breast density and a decrease in sensitivity and specificity of mammography screening [19, 20]. Cessation of HRT could result in a short-term increase in breast cancer incidence, adding particular complexity to analyze the recent changes observed in France. Before 2002, breast cancer incidence has risen with an increase of almost 3% per year [2]. It is impossible to sort out the effects of changes in screening and HRT use. These effects are superimposed upon birth cohort patterns due to generational changes in reproductive behavior. We observed in France the highest incidence rates among women aged 60-64 years as has been reported in Geneva [21]. France and Switzerland both have high-levels of screening and HRT use at the same period. HRT and screening could explain this shift in age-incidence. After 2002, the rapid fall in HRT coexisted with the development of organized screening. Between 2003 and 2006, HRT prescriptions and breast cancer incidence rates followed parallel tracks of decline for women 55-59 and 60-64 years old. The decline in incidence in France was less dramatic than in the US because of the progressive implementation of screening.

Beyond the age of 65, the number of users decreases and the impact of decline in HRT use on breast cancer incidence is lower. In the 70 to 74 year old age group, changes in screening patterns are sufficient to explain changes in breast cancer incidence after 2002.

In a national survey in 2000, 83% of the users received combined estrogen-progestagen preparations and 17% estrogen only HRT [22]. In France, the range of HRT preparations differs from what is found in the United States and conjugated estrogens and medroxyprogesterone acetate are not prescribed. Breast cancer risk varies according to the types of progestins combined with estradiol [16]. In the French E3N cohort study, the risk was significantly lower with progesterone or dydrogesterone than with other progestagens [23]. However, between 1990 and 2002, less than 50% of women used estrogen-progesterone or estrogen-dydrogesterone combinations. The other therapies combined estradiol with different synthetic progestins. We have no information available on other drugs that can influence breast cancer incidence, such as tibolone, tamoxifen or raloxifene. A small minority of postmenopausal women used these drugs, but they were not reimbursed by Social Security for this clinical indication. Generally in Europe, the pattern of HRT use is different from that in the US. Moreover, there are large disparities in prevalence of HRT use in Europe. France was a high use country like Switzerland, Belgium and Germany. Our study has limitations like other ecological studies. Data do not include information regarding individual patients. The decrease in breast cancer rates for women 55-64 years cannot be attributed exclusively to the decrease in the use of HRT. However, rapid changes in reproductive factors, in environmental exposures or changes in life style factors have not been documented in France. The only breast cancer risk factor that has changed substantially between 2002 and 2004 was HRT. Morever, our results parallel those from the US, Australia, Germany or New Zealand, and we produce results in a large population set. Continued surveillance of breast cancer incidence is warranted in France in the years following large-scale cessation of HRT use. Data from registries with pathology reports, information on receptor status of cancers and studies on the role of different progestins and their duration may allow a better understanding of the complex variations of breast cancer incidence and the impact of HRT. ▼

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