

Disentangling the Roles of Mammographic Screening and HRT in Recent Breast Cancer Incidence Trends in Italy by Analyses Based on Calendar Time and Time Since Screening Activation

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■ **Abstract:** The aim of the study was to evaluate the roles of screening activation and hormone replacement therapy discontinuation on the recent declining breast cancer incidence trends in Italy. We analyzed 41,358 invasive female breast cancers incident during 1991–2004 in six Italian population-based cancer registries. Overall and age-specific incidence trends were evaluated using Joinpoint analysis. In addition to calendar years, data were analyzed on a years-since-screening-activation basis. Annual percentage change of standardized rates was computed. There were statistically significant increasing trends for women 40–44 and 45–49 years that did not change after screening activation. On the contrary, for women 50–69 years old and for those 70+ years, the increasing trends flattened around 2 years after screening activation. The prevalence of hormone replacement therapy use in Italy is and was rather low. In conclusion, the recent tendency toward stabilization observed in Italy for female breast cancer incidence rates in women aged 50 years or more follows the introduction of mammographic screening. ■

Key Words: breast cancer, hormone replacement therapy, incidence, population-based, screening

In the USA, female breast cancer incidence rates showed a sharp decrease from 2002 to 2003. The decrease has been attributed mainly to a reduced use of postmenopausal hormone therapy (HRT) (1), a consequence of the publication of the Women's Health Initiative study that showed increased breast cancer and cardiovascular risk for HRT treated women (2). The same attribution has been made in many other western states (3–5).

The use of HRT in the USA was very widespread. Annual HRT prescriptions, for example, reached 90 million in 1999, representing approximately 15 million women per year and remained stable until June 2002 (6) after which it decreased significantly. The percentage of female Kaiser Permanente Northwest members who were prescribed unopposed estrogen or estrogen-plus-progestin at least once per year in the 45+ age group was around 40–45% in 2000, but was 10–12% in 2006 (1).

Aside from reduced use of HRT, cancer incidence rates may be affected by mammographic screening. On activation, screening increases incidence among screened women because of the anticipated detection of preclinical cancers, but afterwards tends to reduce

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incidence, the cancers that would have been detected having been detected in previous years.

The extent of HRT use varied greatly across Europe. In some areas, such as Geneva where almost half of the 35- to 74-year-old women were current HRT users before the WHI's results were published (7), it was as high as in the USA. In other areas, such as the territory of Italy, HRT was used to a much lesser extent. The adoption of mammographic screening has too varied between countries. In Italy, it is quite widespread and therefore the effect on breast cancer incidence rates of screening may be more relevant in that country than in others such as the USA (1,8).

To contribute to the understanding of recent changes in female breast cancer incidence, we analyzed data held by the Italian Network of Cancer Registries.

MATERIALS AND METHODS

The study was based on the incidence databank of the Italian Network of Cancer Registries (AIRTUM, <http://www.registri-tumori.it>) that collects data from 25 general population-based cancer registries with a combined coverage of 30% of the Italian resident population. We selected those registries with complete data for the period from 1991 to 2004. They are northern Italian registries (Ferrara, Firenze and Prato, Modena, Parma, and Romagna) except for one in the south (Ragusa) and have a combined annual mean coverage of about 2,000,000 women (about 6.7% of the Italian female population).

We considered all ages together (0+ years; overall n : 41,358 invasive breast cancer cases) and four age classes: 40–44 (n : 2,509), 45–49 (n : 3,889), 50–69 (n : 19,575), and 70+ years (n : 13,365).

In most of the covered municipalities, mammographic screening was active for women aged 50–69 years, and screening activation varied from before 1991 (about 20% of the municipalities) to 2000.

We used the Joinpoint Regression program to calculate temporal trends (<http://srab.cancer.gov/joinpoint/>), looking for points in time where the trend significantly changed from a straight line (9). The analysis is based on standardized incidence rates and trend is expressed as annual percent change (APC).

The trend analysis was carried out on two different time axes, the calendar time, from 1991 to 2004 and the time (years) since mammographic screening activation. In the latter analysis, we defined the year of

screening activation for each municipality according to data provided by the IMPACT study, a collaborative Italian project which studies the effects of mammographic screening on population (10). If in a municipality screening started in 1997, that year was considered the first year of screening activity, 1998 the second and so on. To focus on screening activation, we restricted the analysis to the 6 years before (from –5 to 0) and 8 years after activation. Therefore, for those registries (or one or more municipalities within a registry) that did not have screening activity during 1991–2004 only the six most recent years of incidence were considered, but, on the other hand, if the year of screening activation was 1991 or earlier, only the 8 years from screening activation were included (i.e., from +1 to +8).

RESULTS

Figure 1 shows the Joinpoint analysis by calendar year from 1991 to 2004.

The overall trend (all ages included) is fairly stable during the early nineties, but then there is a sharp and statistically significant increase (APC = +5.8%, 95% CI: +4.2 to +7.5) until the late nineties followed by a statistically significant decrease (APC = –1.4%, 95% CI: –2.4 to –0.3).

Individual age classes have different trends. There is a steady statistically significant increase for both 40- to 44-year-old women (APC = +1.3, 95% CI: +0.3 to +2.3) and 45- to 49-year-old women (APC = +2.1, 95% CI: +0.9 to +3.2). The trend for women aged 50–69 years was similar to that for all ages starting with a statistically insignificant decrease followed by a remarkable increase from the mid to the late nineties (APC = +8.0, 95% CI: +5.2 to +10.8) and finishing with a statistically significant decrease (APC = –2.2, 95% CI: –3.8 to –0.6).

The trend for the oldest class (70+ years) shows a significant decrease (APC = –1.3, 95% CI: –2.5 to –0.1) from the late nineties after a period of increase (APC = +2.6, 95% CI: +1.4 to +2.7).

Mammographic screening was active in 239 municipalities (95.2% of the municipalities covered by the registries), and in more than 50% of them the year of activation was between 1997 and 1999. The age range of the target population in the analyzed areas was 50–69 years with an active invitation every 2.5 years. Table 1 shows the number of cases stratified by age and period (prescreening and screening). Figure 2,

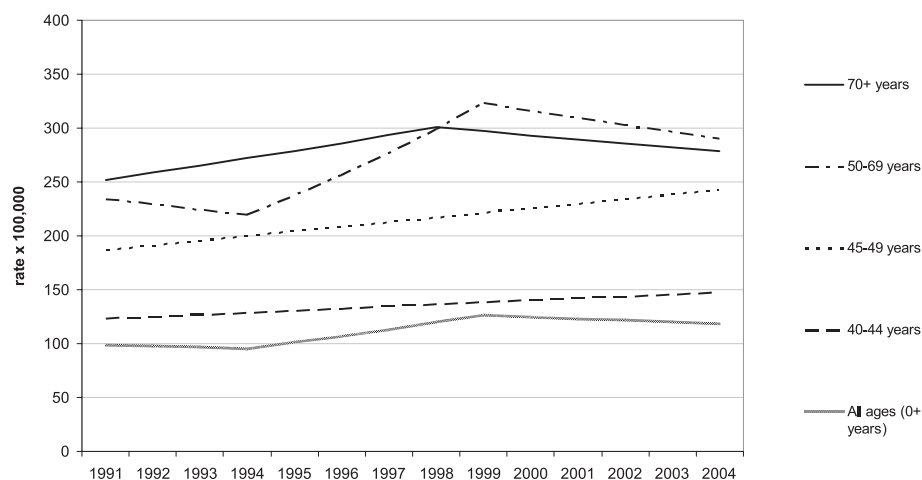


Figure 1. Female breast cancer incidence trends according to age and calendar years. Standardized (European Standard Population) rates.

Period	0–39 years	40–44 years	45–49 years	50–69 years	70+ years	All ages
Prescreening	689	900	1,371	6,231	4,362	13,553
Screening	1,331	1,609	2,518	13,344	9,003	27,805
Total	2,020	2,509	3,889	19,575	13,365	41,358
Year of incidence						
1991	99	156	224	1,119	705	2,303
1992	110	163	255	1,146	740	2,414
1993	115	154	249	1,220	797	2,535
1994	111	147	231	1,108	863	2,460
1995	146	186	267	1,181	903	2,683
1996	132	156	276	1,353	898	2,815
1997	131	157	297	1,389	1,011	2,985
1998	157	190	267	1,544	1,058	3,216
1999	159	189	308	1,692	1,035	3,383
2000	169	188	263	1,649	1,051	3,320
2001	183	196	297	1,568	1,039	3,283
2002	179	205	321	1,544	1,117	3,366
2003	168	209	317	1,547	1,057	3,298
2004	161	213	317	1,515	1,091	3,297

Table 1. AIRTUM Female Breast Cancer, Number of Cases by Age and Period (Prescreening, Screening)

which shows the Joinpoint analysis by time since screening activation, does not evidence any change attributable to screening activation in the increasing trend of the younger women, 40–44 years ($APC = +1.6$, 95% CI: +0.5 to +2.8) and 45–49 years ($APC = +2.5$, 95% CI: +1.2 to +3.9). However, for the 50- to 69-year-old class incidence rates change around the second year after screening activation, shifting from an increasing trend ($APC = +7.6$, 95% CI: +3.6 to +11.7) to a decreasing one ($APC = -2.1$, 95% CI: -6.3 to +2.4). A similar pattern is seen for the oldest class in which an increasing trend up to the first 2 years after screening activation ($APC = +3.2$, 95% CI: +2.0 to +4.3) is followed by a flattening ($APC = -1.0$, 95% CI: -2.4 to +0.4). The trend for

all ages together mirrors that for 50–69 and 70+ years old women.

DISCUSSION

In the present study, female breast cancer incidence rate trends tended to level out from the end of the nineties after a period of increase.

Although the Joinpoint analysis identifies one or more points around which trend changes, its results should be interpreted as periods instead of points of change, but even with this in mind we did not identify any change comparable to the sharp decrease highlighted in the USA between 2002 and 2003 (1). On the contrary, incidence seems to have changed

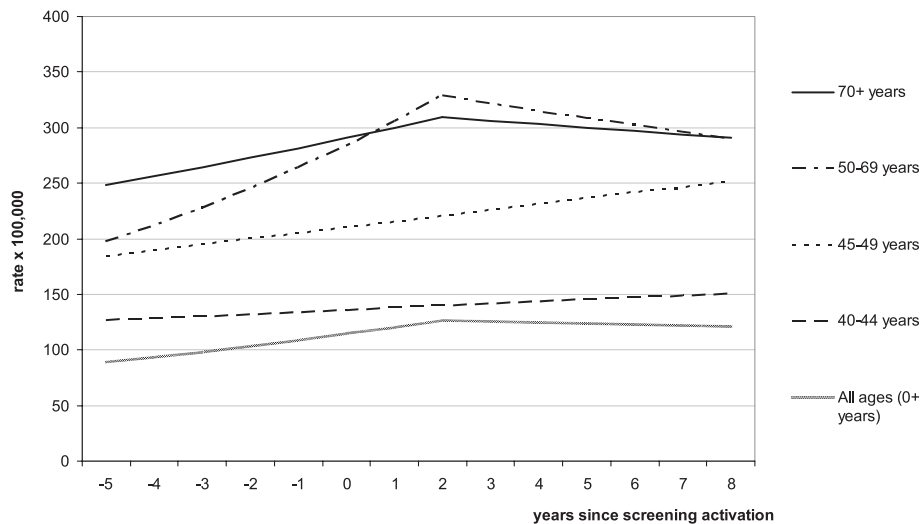


Figure 2. Female breast cancer incidence trends according to age and time since screening activation. Standardized (European Standard Population) rates.

several years before at the end of the nineties, a period corresponding in the analyzed dataset with the peak in activation of mammographic screening programmes.

The all age trend is very similar to that for Italian women aged 50 years or more, but quite dissimilar to that for younger women where there is a significant increasing trend in incidence rates with a rate of increase in standardized rates of about 1–2% every year. The increase of incidence among these younger women, and also those aged 0–39 (data not shown), is worrying as it shows an increase in the diffusion of risk factors in these age classes (e.g., westernization in reproductive factors, and obesity) and presages a future stability in the relevance of breast cancer among women. These trends for women younger than 50 years differ from the USA experience. In fact, SEER data showed, for the same period 1991–2004, a stable trend for women aged 0–44 years and statistically significant decreasing trend for those aged 45–49 years (<http://seer.cancer.gov>).

The reasons for the change in the all age incidence trend around the end of the nineties could be at least twofold. Firstly, a discontinuation in use of HRT as occurred in the USA in 2002 and 2003, but for this to be arguable there would need to be a previous high prevalence of HRT use and a relevant discontinuation. Only sparse data are available for the diffusion of HRT use in Italy. A study on colon and rectal neoplasms showed that during 1992–1996 the prevalence among 45- to 74-year-old women of those

who had ever used HRT was about 8.5% (11). A few years later, a survey of 42,464 women (mean age 54 years) attending a network of menopause clinics in Italy showed HRT use in 11.6% of the sample (12). In more recent years, a survey of women aged 45+ years carried out in the 12 local health units of the Veneto region showed that the prevalence of HRT users was 7% in 2002, 6.2% in 2003, and 5% in 2004 (13). In the city of Milan according to the HRT prescriptions file for women aged 50–69 years the estimated prevalence of users was 12.4% in 2003, 10.3% in 2004, 8.4% in 2005, and 8.2% in 2006 (Dr. A. Russo, personal communication). As found in the FRiCaM study the proportion of HRT users is higher for selected subsets of women. Aimed at evaluating risk factors for breast cancer, FRiCaM was a study of about 140,000 women who attended mammographic screening and who were resident in the areas of Turin, Florence, and Milan in the period 2003–2006. The overall prevalence of HRT use was 25.2%, but among those with low and high education it was 13% and 27%, respectively (Dr. A. Russo, personal communication). It has been confirmed that women of higher socioeconomic status or education report more frequent use of HRT (11). In Modena province data on HRT annual prescriptions in the period 2002–2006 were obtained through the pharmaceutical service of the local health unit. The data was categorized—estrogen-based, progesteron-based, and estrogen/progesteron combination—and for each category the number per year was calculated.

The consumption of estrogen-based HRT decreased between 2002 and 2006 from more than 60,000 to less than 30,000 number of pieces, with a small reduction in the progesteron-based use and a substantial maintaining of estrogen/progesteron combination.

Although in Italy we have no national surveys, all the available data shows that the prevalence of use of HRT was sensibly lower than in the USA (1,6), and it may be estimated at about 10% with a decreasing trend in recent years. Moreover, the decrease was not as sharp as in the USA where there was a 50% reduction per year from 2001 to 2003 (14). In fact, the reduction in the number of prescriptions written was quite steady at 15.3% in 2002 in comparison to 2001, 18% from 2003 and 2002, 20% from 2004 and 2003, 13% from 2005 and 2004, and 18% from 2006 and 2005 (http://www.agenziafarmaco.it/ATTIVITA_EDITORIALE/gotopage_section318e.html). We feel that it is unlikely that a smooth reduction of use of HRT in a rather small percentage of the user population can have affected overall incidence rates.

But HRT discontinuation is not the only possible explanation for the observed change in female breast cancer incidence: the other may be mammographic screening. We carried out a Joinpoint analysis according to time since screening activation to highlight changes related to the introduction of screening. Our analysis confirmed that incidence trends changed accordingly to the theoretical curve for women 50–69 years (that is the screening target population). In fact, there was a peak of incidence just after the first round followed by a decrease (a round requires 2–3 years for completion in large populations). The decrease in incidence curve was predictable by application of estimated lead-times, which varies from 2 to 6 years in different age-groups.

Additionally, the group of women older than 70 years shows a stabilization of rates after screening activation probably due to the gradual inclusion of subjects screened during their late sixties.

In contrast with these observations, screening activation had no apparent effect for women younger than 50 years.

Mammographic screening has spread widely in Italy since the pioneer programs in the 1980s. In recent years almost 2/3 of the target population (women aged 50–69 years), mainly in north and central Italy, have been involved in active screening programmes. (<http://www.osservatorionazionale screening.it>).

In Italy the diffusion of both HRT use and screening programmes increased concurrently. Therefore, it is difficult to disentangle their independent effects. However, in Italy the decreasing breast cancer incidence trend started around the end of the 1990s before the publication of the WHI results. Moreover, in Italy there were a rather low proportion of HRT users and a steady decline in their number over time without a sudden drop. These observations support an argument for a major effect of screening diffusion on breast cancer incidence trend rather than of HRT discontinuation. Screening diffusion has also been claimed for explaining incidence trends in the city of Turin (8). Screening diffusion in Italy may be more relevant than in the USA (15).

The analyzed dataset is not a random sample of the Italian population. In fact, it is more representative of the north of Italy with an area from the south. This geographical selection may have enhanced the effect of mammographic screening because the diffusion of screening in the analyzed areas is greater than the average for the country, except for the analyzed area in the south of Italy.

However, the prevalence of HRT decreases in Italy from north to south (estimates for 2000 were 11.4% in northeastern, 8% in central, and 5.1% in southern Italy (16). Therefore, in a random Italian sample with a wider southern population the expected effect of HRT discontinuation would be even lower than in the present study.

In conclusion, in Italy the recent tendency toward stabilization and even reduction observed for female breast cancer incidence rates, in women aged 50 or more years, seems to have resulted more from the introduction of mammographic screening than to changes in HRT use.

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