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EPIDEMIOLOGY

# Changing pattern of age-specific breast cancer incidence in the Swiss canton of Geneva

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**Abstract** Hormone replacement therapy (HRT) use declined sharply after mid-2002, when the Women's Health Initiative trial reported an association between breast cancer occurrence and HRT. Hypothesized mechanism behind this association is that HRT promotes growth of pre-existing small tumors, leading to earlier tumor detection. We evaluated the impact of the sudden decline in HRT use on age distribution of breast cancer in Geneva. We included all incident breast cancer cases recorded from 1975 to 2006 at the Geneva cancer registry. We calculated mean annual incidence rates per 100,000 for 2 year periods for three age groups and assessed temporal changes by joinpoint regression. We compared age-specific incidence curves for different periods, reflecting different prevalence rates of HRT use. After increasing constantly between 1986 and 2002 among women aged 50–69 years [annual percent change (APC): +4.4, $P < 0.0001$], rates declined sharply after 2003 (APC: −6.0; $P = 0.0264$). Age-specific breast cancer rates changed dramatically with changes in prevalence of HRT use. During low HRT prevalence, breast cancer incidence increased progressively with age, when HRT prevalence was reaching its maximum (1995–2002), higher rates were seen in 60- to 64-year-old women, with a concomitant decrease in risk among elderly. After the sudden decline in HRT use, the incidence peak diminished significantly and incidence increased again with age. Following the abrupt decline in HRT use in Geneva, breast cancer incidence rates among post-menopausal women decreased considerably with striking changes in age-specific incidence rates before, during and after the peak in HRT prevalence.

**Keywords** Breast cancer · Diagnosis · Incidence · Hormone replacement therapy

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## Introduction

After that the Women's Health Initiative (WHI) randomized controlled trial in 2002 reported an increased breast cancer risk among women using hormone replacement therapy (HRT) [1, 2], HRT use and breast cancer incidence among post-menopausal women showed an important decline in several countries, including USA, Belgium, France, Australia, United Kingdom, and Germany [3–7].

In Geneva, Switzerland, breast cancer incidence rates are among the highest in Europe, and so is the prevalence of HRT use (46% of women were current users in 2000–2002) [8, 9]. Following the publication of the WHI and the results of the Million Women Study in 2003, the use of HRT among post-menopausal women declined abruptly in Geneva to 31% [8], while mammography screening continued to expand [10–12].

The biologic mechanism proposed to explain HRT influence on breast cancer risk is that HRT acts as promoter of already existing tumor cells [13] leading to an advance in the presentation of these cancers. We have previously reported on the change in breast cancer age-specific curve in Geneva, with the appearance of a peak of incidence among women aged 60–64 years and a subsequent decline in the rates of older women. Our hypothesis for such change was the increasing prevalence of use of HRT during the 1990s [12].

The present study reports changes in breast cancer incidence and age distribution following the decrease in the HRT use among the female population of Geneva. This report also presents, for the first time, the effect of change on the age distribution curve.

## Materials and methods

We used data from the Geneva cancer registry, which records information on all incident cancer cases that occur in the canton ($\sim$450,000 inhabitants). Registration is based on public and private sources of information and is very accurate, as attested by the low percentage (<2%) of cases recorded from death certificates only [14].

We considered all incident breast cancer cases diagnosed from 1976 to 2006. We calculated the mean annual incidence rates per 100,000 women for 2 year periods for three age groups: 25–49 years (pre-menopausal), 50–69 years (early post-menopausal), and $\geq$70 years (late post-menopausal). We assessed trends in age-specific incidence rates using joinpoint regression. This procedure fits a model based on a minimum number of joinpoints that are the points where statistically significant changes in incidence rates occur. Joinpoint regression assumes a log-linear model, starts with a model with zero joinpoints and adds more joinpoints, up to three, until the new model has a statistically significant difference compared to the previous one. The generation of models and the test of significance were performed using the Monte Carlo Permutation method program (version 3.0) [15].

We applied the difference in breast cancer incidence of women aged 50–69 years between 2005–2006 and 2002–2003 to women of the same age group resident in the canton in order to estimate the "deficit" of breast cancer patients in the period following the decline in HRT use (2003–2006).

To illustrate the changes in the age incidence curve by period, we calculated age-specific incidence rates by 5 year groups for four different periods (1975–1989; 1995–1999; 2001–2003; and 2005–2006).

## Results

### Trends of incidence rates by age group

Overall, breast cancer incidence rates progressively increased between 1975 and 2004, and then decreased in 2005–2006 to levels observed in 1997–1998 (Fig. 1). The overall annual percent change (APC) was 1.7% ($P < 0.0001$; Table 1). Among women aged 50–69 years, breast cancer incidence rates were stable from 1975 to 1986, increased sharply until 2001–2002, and then suddenly decreased in 2003–2004 (Fig. 1). In this group, the APC was +4.4% between 1986 and 2002 ($P < 0.0001$), while between 2002 and 2006 the incidence rates decreased 6.0% yearly ($P = 0.0264$; Table 1). In contrast, in the age group $\geq$ 70 years, rates were relatively constant for the whole period, with a non-significant APC of −0.03%. In the age group < 50 years, breast cancer rates were relatively constant until 2003–2004, and then started to increase (APC: +0.9, $P = 0.0012$; Fig. 1; Table 1).

Among women aged 50–69 years, the mean annual incidence rates were 430.7/100,000 in 2001–2002 and only 341.4/100,000 in 2005–2006, respectively.

Applying this incidence rate difference to the resident population of the same age group, we estimated a "deficit" of 45 new breast cancer cases per year among post-menopausal women aged 50–69 year, representing 21% of annual cases in this age group and 11% of all breast cancer cases in Geneva.

### Age-specific incidence rates

Figure 2 gives the age-specific breast cancer incidence rates according to period. For the period 1975–1989, breast cancer incidence progressively increased with age with the typical slope down around 50 years (Clemmensen's hook). In the period after 1995, an incidence peak gradually appeared around the age of 60–64 years, while the incidence for older women moved down. This last pattern was most evident in 2001–2003 when the rate among 60- to 64-year-old women culminated. In 2005–2006, the curve changed shape again, with a reversal of the peak of incidence rates among women aged 60–64 years, accompanied by an increase in breast cancer rates among older women.

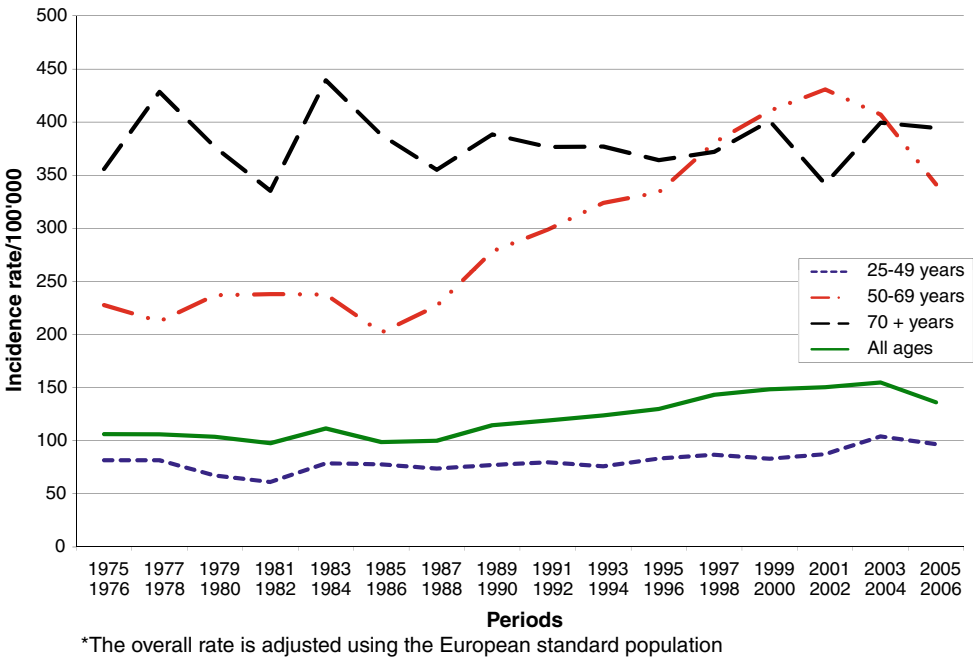


**Fig. 1** Breast cancer incidence rates by 2 year periods according to age-groups. Geneva 1975–2006

**Table 1** Trends of age-adjusted breast cancer incidence rates

| 25–49 years old | | | 50–69 years old | | | 70+ years old | | | All ages | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Period | APC | *P* value | Period | APC | *P* value | Period | APC | *P* value | Period | APC | *P* value |
| 1975–2006 | +0.9 | 0.0012 | 1975–1986 | −0.2 | 0.7643 | 1975–2006 | −0.03 | 0.8846 | 1975–2006 | +1.7 | 0.0001 |
| | | | 1986–2002 | +4.4 | 0.0001 | | | | | | |
| | | | 2002–2006 | −6.0 | 0.0264 | | | | | | |

Geneva 1975–2006

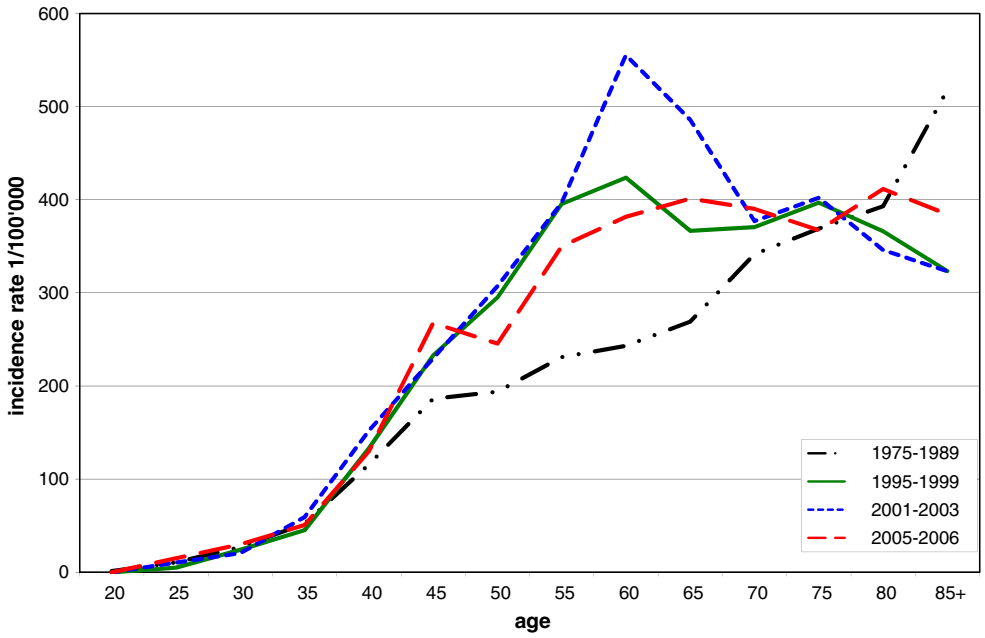


**Fig. 2** Invasive breast cancer incidence rates by age and period, Geneva 1975–2006

## Discussion

Following the abrupt decline of HRT use in the canton in 2003, we observed an important decrease in breast cancer incidence rates and an impressive change of the shape of the age-specific incidence curve. The incidence rates of early post-menopausal women decreased by 6% per year from 2002, similar to observations made in USA, Germany, and Australia [3–5].

Previously, we reported that the age-specific breast cancer incidence curve in Geneva peaked around 60–64 years, was limited to estrogen positive tumors and women who used HRT independently of their use of mammography screening [12]. Furthermore, we underlined the inexistence of such change in the Netherlands, where use of mammography is very high and HRT use very low (only 13%) [10]. The current study shows, for the first time, a reversal of this incidence peak, as well as a new increase in older women. The reversion to previous traditional age incidence curve and the decline in breast cancer incidence limited to early post-menopausal women further supports the causal link between HRT and change in breast cancer incidence.

The mechanism behind the effect of HRT on breast cancer risk is not fully understood. The hypothesis is that HRT acts as a 'fertilizer' on pre-existing small breast tumors, meaning that only women who already have latent breast cancers will develop overt disease when using HRT [13]. Arguments in favor of this hypothesis are the very short delay between use of HRT and individual increased risk of breast cancer, change in HRT use and change in incidence rates and the fact that the excess concerns mainly estrogen positive breast cancers, which are more reactive to hormonal changes [16].

Only few data is currently available on the impact of the decline of HRT use on the histological type of breast cancer. The association with HRT use is stronger for lobular carcinoma than for ductal carcinoma [17, 18]. In Belgium, Vankrunkelsven et al. [7] found a larger decline in invasive lobular than in ductal carcinomas, while inverse results were found in the USA [19]. For Geneva, we previously reported a disproportionate increase in lobular cancer incidence during the period 1976–1999. This was particularly relevant among women aged 50–59 years, born after 1944 [20]. However, in the present analysis, we observed no decline of incidence of lobular cancer overall or in early post-menopausal women (data not shown).

Although we are aware that causality cannot be established by this kind of descriptive study, alternative explanations of such epidemiologic pattern seem unlikely.

Screening rates have slowly increased in Geneva during the last years [11]. Sudden changes in lifestyle or environmental risk factors have not been documented and would not in any case explain such a strong and rapid change. Conversely, a reduction of exposure to HRT, especially among those highly hormone sensitive tumors, would stop or slow their growth, leading to a diagnosis at a later age [21].

In conclusion, we found that in Geneva, breast cancer incidence rates decreased considerably following the abrupt reduction in HRT use and that this decline was limited to post-menopausal women. Age-specific incidence curves showed completely different patterns before, during, and after the decrease in the HRT use. If the role of HRT is limited to fertilization of existing tumors, we could expect a new increase in cases among older women and a return to the traditional incidence curve by age in the years to come.

This study demonstrates how use of HRT can dramatically change the natural history of breast cancer.

## References

1. Beral V (2003) Million women study collaborators: breast cancer and hormone-replacement therapy in the million women study. Lancet 362(9382):419–427
2. (2002) Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the women's health initiative randomized controlled trial. JAMA 288(3): 321–333
3. Ravdin PM, Cronin KA, Howlader N, Berg CD, Chlebowski RT, Feuer EJ, Edwards BK, Berry DA (2007) The decrease in breast-cancer incidence in 2003 in the United States. N Engl J Med 356(16):1670–1674
4. Katalinic A, Rawal R (2008) Decline in breast cancer incidence after decrease in utilisation of hormone replacement therapy. Breast Cancer Res Treat 107(3):427–430
5. Canfell K, Banks E, Clements M, Kang YJ, Moa A, Armstrong B, Beral V (2009) Sustained lower rates of HRT prescribing and breast cancer incidence in Australia since 2003. Breast Cancer Res Treat
6. Seradour B, Allemand H, Weill A, Ricordeau P (2009) Changes by age in breast cancer incidence, mammography screening and hormone therapy use in France from 2000 to 2006. Bull Cancer 96(4):E1–E6
7. Vankrunkelsven P, Kellen E, Lousbergh D, Cloes E, Op de Beeck L, Faes C, Bruckers L, Mertens R, Coebergh JW, Van Leeuwen FE, Buntinx F (2009) Reduction in hormone replacement therapy use and declining breast cancer incidence in the Belgian province of Limburg. Breast Cancer Res Treat
8. Morabia A, Costanza MC (2006) Recent reversal of trends in hormone therapy use in a European population. Menopause 13(1):111–115
9. Cancer incidence in five continents (2002) International Agency for Research on Cancer, vol VIII. IARC Scientific Publications no 155, Lyon
10. Verkooijen HM, Koot VC, Fioretta G, van der Heiden M, Schipper ME, Rapiti E, Peeters PH, Peterse JL, Bouchardy C (2008) Hormone replacement therapy, mammography screening and changing age-specific incidence rates of breast cancer: an ecological study comparing two European populations. Breast Cancer Res Treat 107(3):389–395
11. Observatoire suisse de la santé Obsan (2006) La santé en Suisse romande et au Tessin en 2002, 1 June 2009
12. Bouchardy C, Morabia A, Verkooijen HM, Fioretta G, Wespi Y, Schafer P (2006) Remarkable change in age-specific breast

cancer incidence in the Swiss canton of Geneva and its possible relation with the use of hormone replacement therapy. BMC Cancer 6(1):78
13. Dietel M, Lewis MA, Shapiro S (2005) Hormone replacement therapy: pathobiological aspects of hormone-sensitive cancers in women relevant to epidemiological studies on HRT: a mini-review. Hum Reprod 20(8):2052–2060
14. Bouchardy C (2002) Switzerland, Geneva. In: Parkin DM, Whelan SL, Ferlay J, Teppo L, Thomas DB (eds) Cancer incidence in five continents, vol VIII. International Agency for Research on Cancer, Lyon, pp 448–449
15. National Cancer Institute (2007) Statistical research and applications. Joinpoint Regression Program, 1 May 2009
16. Glass AG, Lacey JV Jr, Carreon JD, Hoover RN (2007) Breast cancer incidence, 1980–2006: combined roles of menopausal hormone therapy, screening mammography, and estrogen receptor status. J Natl Cancer Inst 99(15):1152–1161
17. Reeves GK, Beral V, Green J, Gathani T, Bull D (2006) Hormonal therapy for menopause and breast-cancer risk by histological type: a cohort study and meta-analysis. Lancet Oncol 7(11):910–918
18. Li CI, Malone KE, Porter PL, Weiss NS, Tang MT, Cushing-Haugen KL, Daling JR (2003) Relationship between long durations and different regimens of hormone therapy and risk of breast cancer. JAMA 289(24):3254–3263
19. Li CI, Daling JR (2007) Changes in breast cancer incidence rates in the United States by histologic subtype and race/ethnicity, 1995 to 2004. Cancer Epidemiol Biomarkers Prev 16(12): 2773–2780
20. Verkooijen HM, Fioretta G, Vlastos G, Morabia A, Schubert H, Sappino AP, Pelte MF, Schafer P, Kurtz J, Bouchardy C (2003) Important increase of invasive lobular breast cancer incidence in Geneva, Switzerland. Int J Cancer 104(6):778–781
21. Krieger N (2008) Hormone therapy and the rise and perhaps fall of US breast cancer incidence rates: critical reflections. Int J Epidemiol 37(3):627–637