Breast Cancer Res Treat (2008) 107:389–395
DOI 10.1007/s10549-007-9554-3

EPIDEMIOLOGY

Hormone replacement therapy, mammography screening and changing age-specific incidence rates of breast cancer: an ecological study comparing two European populations

H. M. Verkooijen · V. C. M. Koot · G. Fioretta · M. van der Heiden · M. E. I. Schipper · E. Rapiti · P. H. M. Peeters · J. L. Peterse · C. Bouchardy

Received: 15 February 2007 / Accepted: 19 February 2007 / Published online: 13 March 2007

Abstract
Background In 2003, for the first time, US breast cancer incidence rates have fallen. Experts argue whether this is due to the reduced uptake of screening mammography or to lower use of Hormone Replacement Therapy (HRT). This study aims to disentangle the respective impact of screening and HRT on age-incidence rates and histology of breast cancer, by comparing two populations with comparably high levels of screening mammography, but with different prevalence of HRT.
Methods We included all invasive breast cancers recorded at the Geneva cancer registry (n = 4,909) and the Netherlands Cancer Registry (n = 152,428) between 1989–2003. We compared age-specific incidence rates and trends in histological subtyping between the two populations.
Results Between 1989–1991, incidence rates increased with age in both populations. In 2001–2003, women aged 60–64 years showed highest incidence rates in Geneva, while in the Netherlands incidence rates continued to increase with age. The annual increase in ductal cancer incidence was similar in the Netherlands (2.3%) and Geneva (2.5%), but the annual increase in lobular cancer was sharper in Geneva (10%) than in the Netherlands (5%).
Conclusion The sharp differences in age distribution and histological subtyping of breast cancer between two European populations are not attributable to screening, since both populations have a high uptake of mammography screening. Since the prevalence of HRT use is very high in Geneva and rather low in the Netherlands, HRT may explain these discrepancies. However, other etiological factors and differences in histological assessment may also have played a role.

Keywords Breast cancer · Hormone replacement therapy · Incidence · Population-based · Screening

H. M. Verkooijen · G. Fioretta · E. Rapiti · C. Bouchardy
Geneva Cancer Registry, Institute for Social and Preventive Medicine, Geneva University, 55 Boulevard de la Cluse, Geneva 1205, Switzerland

H. M. Verkooijen (✉)
Department of Community Occupational and Family Medicine, National University of Singapore, 16 Medical Drive, Singapore 117597, Singapore
e-mail: cofhmv@nus.edu.sg

V. C. M. Koot · M. van der Heiden
Comprehensive Cancer Center Middle Netherlands, Catharijnesingel 55, Utrecht, GD 3511, The Netherlands

V. C. M. Koot · M. van der Heiden
Association of Comprehensive Cancer Centers, P.O. Box 19001, Utrecht, DA 3501, The Netherlands

M. E. I. Schipper
Department of Pathology, University Medical Center Utrecht, P.O. Box 85500, Utrecht, GA 3508, The Netherlands

P. H. M. Peeters
Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, P.O. Box 85500, Utrecht, GA 3508, The Netherlands

J. L. Peterse
Department of Pathology, Netherlands Cancer Institute, Plesmanlaan 121, Amsterdam, CX 1066, The Netherlands

Introduction

In 2003, for the first time in recent history, the incidence of breast cancer has come down in the United States [1]. Experts argue whether this is due to the lower uptake of screening mammography following publications questioning

its effectiveness [2, 3] or because of the decreased use of Hormone Replacement Therapy (HRT) following reports on its association with increased breast cancer and cardiovascular risks [4, 5]. Other reasons, including other medications potentially linked to breast cancer risk, may have influenced breast cancer rates as well.

Within Europe, there are large disparities in uptake of screening mammography and prevalence of HRT use. This provides unique opportunities for ecological studies on the respective impact of screening and HRT on breast cancer incidence trends.

Over recent years, several studies have reported changes in breast cancer incidence, including increasing incidence rates, shifts in age distribution of breast cancer and disproportionate rises in lobular cancer rates. In many European countries, incidence rates of invasive breast cancer have increased sharply following the introduction of organized screening programs [6–8]. In addition, there have been changes in age-distribution of breast cancer. Classically, the risk of breast cancer increases with age, but reports from the United States, Switzerland, Finland, Denmark and Sweden [9–13] have shown that this classical pattern is changing. In these populations, highest rates are no longer observed among older women, but among women in their early sixties. Mechanisms for this shift are not yet well understood. Recently, we published population-based data from the Swiss canton of Geneva which was highly suggestive of a key role of hormone replacement therapy (HRT) in the change in age-specific breast cancer incidence [9]. This study contradicted those of Hemminki et al. who attributed the change in age-incidence rates in Sweden and other European countries to the use of mammography screening [12, 13].

In parallel with the shift in age-specific incidence in several countries, invasive lobular cancer rates have increased sharply, particularly during the nineties [14–17]. The increasing use of HRT during the eighties and nineties has been proposed as the reason of the increase in lobular cancer incidence [18–20]. Nevertheless, improved diagnostic techniques, increased diagnostic activity (screening) and changes in criteria for histological assessment may also have played a role.

In the current study, we compare trends in incidence rates, age-specific incidence rates and histological subtyping of breast cancer between Geneva Switzerland and the Netherlands. Both populations have breast cancer rates that are among the highest in the world [21]. Both countries have a high standard of medical care and large proportions of women undergoing organized or opportunistic mammography screening [8, 22]. The prevalence of HRT during the nineties was, however, quite different. In the Netherlands, 13% of all 49–70 year old women and 19% of the 49–54 year old women were current users of HRT between 1993–1997 [23]. In Geneva, the prevalence of HRT use is particularly high. In 1996, more than 50% of 45–59 year old women were current users of HRT [24]. A more recent study showed that in 2002, 46% of all women between 35 and 74 years were current users of HRT and the average duration of use was 7.8 years [25]. The proportion of current users in the 45–59 year old age group would probably have been much higher.

Materials and methods

For this study, we used data from two population-based cancer registries: the Netherlands Cancer Registry and the Geneva Cancer Registry.

Nationwide cancer registration in the Netherlands started in 1989. The Netherlands Cancer Registry consists of nine regional registries of the Comprehensive Cancer Centres in the Netherlands. It collects data on all malignant neoplasms in the Dutch population. Population data of the Netherlands were obtained from Statistics Netherlands (Central Bureau voor de Statistiek [CBS] Voorburg / Heerlen, the Netherlands). During the study period, the total population of the Netherlands increased from 15 to 16 million persons.

The Geneva Cancer Registry collects information on all incident cases of cancer in the Swiss canton of Geneva since 1970. Populational data for the canton of Geneva were obtained from the Cantonal Population Office (Office Cantonal de la Population) which covers a population of approximately 420,000 inhabitants.

Both cancer registries are notified by pathologists and medical registration offices on the occurrence of every incident case of cancer. Trained registry staff actively retrieves relevant information, using information from medical records and pathology reports. Recorded data include socio-demographic characteristics and tumour characteristics coded according to the International Classification of Diseases for Oncology (ICD-O) and stage at diagnosis [26].

In both populations, we identified all incident cases of invasive breast carcinoma (ICD code 174) diagnosed between 1989 and 2003. Women with pure in situ lesions (ductal carcinoma in situ or lobular carcinoma in situ) were excluded. Histologic review of microscopic slides was not performed.

Breast cancers were classified as ductal carcinoma (ICD-O code 8500), lobular carcinoma (lobular IDC-O code 8520 and 8522) and other (all other cancers including those without microscopic confirmation).

Incidence rates (European age-standardized) according to histological subtype were calculated. Variations in incidence rates were studied by generalised linear regression analyses based on the maximum likelihood method

[27]. Age-specific incidence rates were calculated by 5-years age groups and compared between two periods (1989–1991 and 2001–2003).

Results

Between 1989 and 2003, 152,428 Dutch women and 4909 women from Geneva, Switzerland were diagnosed with invasive breast cancer. In both populations, there was a significant increase in breast cancer incidence: in the Netherlands, the incidence (European age-standardised) went from 105 to 126/100,000 and the average annual increase was 1.3% ($P < 0.05$) (Fig. 1). In Geneva, Switzerland, the incidence went from 114 to 150/100,000 and the increase was 2.4% ($P < 0.001$) per year.

In the early years of the study period (1989–1991), age-specific incidence increased with age in both populations and highest rates were observed among the 80–84 years old in the Netherlands and among women older than 85 years in Geneva (Fig. 2 panel A).

Between 2001 and 2003, the age distribution of breast cancer was very different between the two populations (Fig. 2 panel B). In Geneva, an incidence peak appeared among women aged 60–64 years: breast cancer rates no longer increased with age, but were highest in middle-aged women and reduced in the elderly. The incidence rates for women aged 60–64 years almost doubled and rose from 289/100,000 in 1989–1991 to 552/100,000 in 2001–2003. For women older than 85 years, the breast cancer incidence rates dropped from 425 to 323/100,000.

In 2001–2003, in the Netherlands, there was still the classical pattern, with highest breast cancer rates in the oldest age categories. Breast cancer rates for women aged 60–64 years increased moderately from 255/100,000 in 1989–1991 to 321/100,000 in 2001–2003. There was no decrease in incidence among women older than 80 years.

In Geneva, 73% of the patients (3573) had ductal histology, 11% (530) lobular histology and 16% (806) other histological subtypes. In the Netherlands, 65% of the patients (98,962) had ductal cancer, 15% (22,112) had lobular cancer and 21% (31,354) had other histological subtypes.

In the Netherlands, the invasive ductal cancer rates went from 67 to 89/100,000 between 1989 and 2003 and the average annual increase was 2.2% ($P < 0.01$) (Fig. 3, panel A). In the same period in Geneva, the ductal cancer incidence went from 87 to 116/100,000 between 1989 and 2003 and the average annual increase was 2.5% ($P < 0.001$).

The trend in invasive lobular cancer incidence was different between the two populations (Fig. 2, panel B). In the Netherlands, the incidence of invasive lobular cancer increased from 13 to 19/100,000 between 1989 and 2003 with a mean annual increase of 3.1% per year ($P < 0.05$). In Geneva, the increase of invasive lobular cancer incidence was much sharper (9.1% per year, $P < 0.001$) and went from 7 to 20/100,000 between 1989 and 2003.

In the Netherlands, the incidence of other histological subtypes decreased from 26 to 18/100,000 (mean annual decrease of 3.2%, $P < 0.01$) and in Geneva from 21 to 14/100,000 between 1989 and 2003 (mean annual decrease 3.0%, $P < 0.05$) (Fig. 3, panel C).

In Geneva, the increase in ductal cancer can be completely attributed to an increase in incidence among 55–69 year old women (Fig. 4 panel A). Especially for women aged 60–64 years, the ductal cancer incidence almost doubled and increased from 225 to 432/100,000 between 1989–2003. In the Netherlands, ductal cancer rates moderately increased in all age categories after 45 years. Only for 75–79 year old women there was a deficit of cases between 2001–2003, due to intensive screening in previous age categories. In 2001–2003, the absolute difference in ductal cancer rates between Geneva and Dutch 60–64 year olds was eminent: 432 *versus* 234 /100,000 respectively.

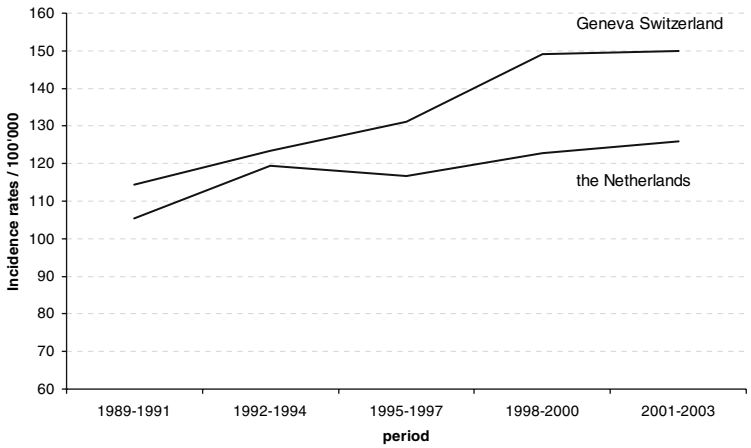

Fig. 1 Incidence rates (European age standardized) of breast cancer for the Netherlands and Geneva, Switzerland, 1989–2003

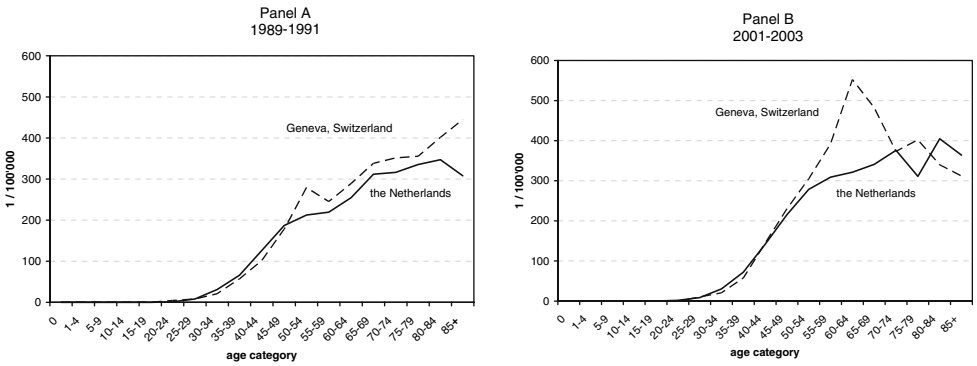

Fig. 2 Age-specific incidence of breast cancer in the Netherlands and Geneva, Switzerland for periods 1989–1991 (panel **A**) and 2001–2003 (panel **B**)

Also for lobular cancer, there were important differences in age distribution between the two populations (Fig. 4, panel B). In Geneva, lobular incidence rates increased sharply for women aged 50–74 years, whereas no major changes occurred for women under 50 years and those older than 80 years. Particularly sharp increases were seen among women aged 60–74 years. In the Netherlands, lobular incidence rates increased for all women after the age of 45 years, and the highest lobular cancer incidence increases were seen among the very old women. In 2001–2003, absolute differences in lobular cancer rates between Genevese and Dutch women were most pronounced for the age categories 60–64 years (76 versus 49/100,000 respectively) and 85 years and older (11 versus 51/100,000 respectively).

In Geneva, the decrease in incidence of other histological subtypes was mostly attributable to a sharp decrease among the very old women (Fig. 4, panel C). In the Netherlands, the incidence of other histological subtypes decreased for all age categories to the same extent and in 2001–2003, Dutch and Genevese women had similar rates of other histologies.

Discussion

In this study we have shown some intriguing differences in age distribution and histological subtyping of breast cancer between two populations with high incidence rates of breast cancer. Firstly, there was a compelling shift in age distribution of breast cancer incidence in Geneva, which was completely absent in the Netherlands. Secondly, the incidence of lobular cancer increased more sharply in Geneva than in the Netherlands, while ductal cancer rates increased to the same extent. The 10% increase in lobular cancer in Geneva was due to a sharp increase in 50–74 year olds, while in the Netherlands, lobular cancer incidence increased more or less proportionately in all age groups after 45 years. In Geneva, the 2.5% annual increase in ductal cancer incidence was exclusively due to an almost doubling of the incidence of 55–69 year olds, while in the Netherlands, the 2.2% annual ductal cancer incidence increase could be attributed to a proportionate increase in all age categories after 45 years.

Some have advocated mammography screening as the explanation of the shift in age-specific breast cancer rates [12, 13]. Using the EUROCAN database, Hemminki and Bermejo compared age-specific incidence rates in several European countries with different attitudes towards, and different levels of implementation of mammography screening in the year 1995 [13]. They observed the typical shift in age-incidence rates in countries with generalization of screening mammography (including France, Sweden, UK and, surprisingly, also the Netherlands), but not in Germany, where organized and opportunistic screening is nearly inexistent. They concluded that screening affects age-incidence trends. They also showed that in Sweden, Norway and Finland, the change in age-incidence rates was progressive during the implementation of the screening programs, suggesting a relation between mammographic coverage and age distribution of breast cancer [13]. However, the changes continued to progress for at least several years after full implementation of mammography screening programs, rendering a key role of screening less likely.

The results of our study practically rule out that screening mammography caused this dramatic change. Screening mammography is very common in the Netherlands, where 80% of the target population (women aged 49–74 years) participate in the national screening program [8]. In Geneva, the breast cancer screening program started only in 1999 and has a relatively low participation rate of approximately 20%. However, since the early nineties, opportunistic screening is common in the canton of Geneva and in the 1997 Swiss National Health Survey over 60% of Geneva women reported to have undergone screening mammography. Nevertheless, it is unlikely that the use of screening mammography in Geneva exceeds the 80% participation rate in the Netherlands. Consequently, increasing use of screening mammography is not a plausible explanation for the shift in age distribution of breast

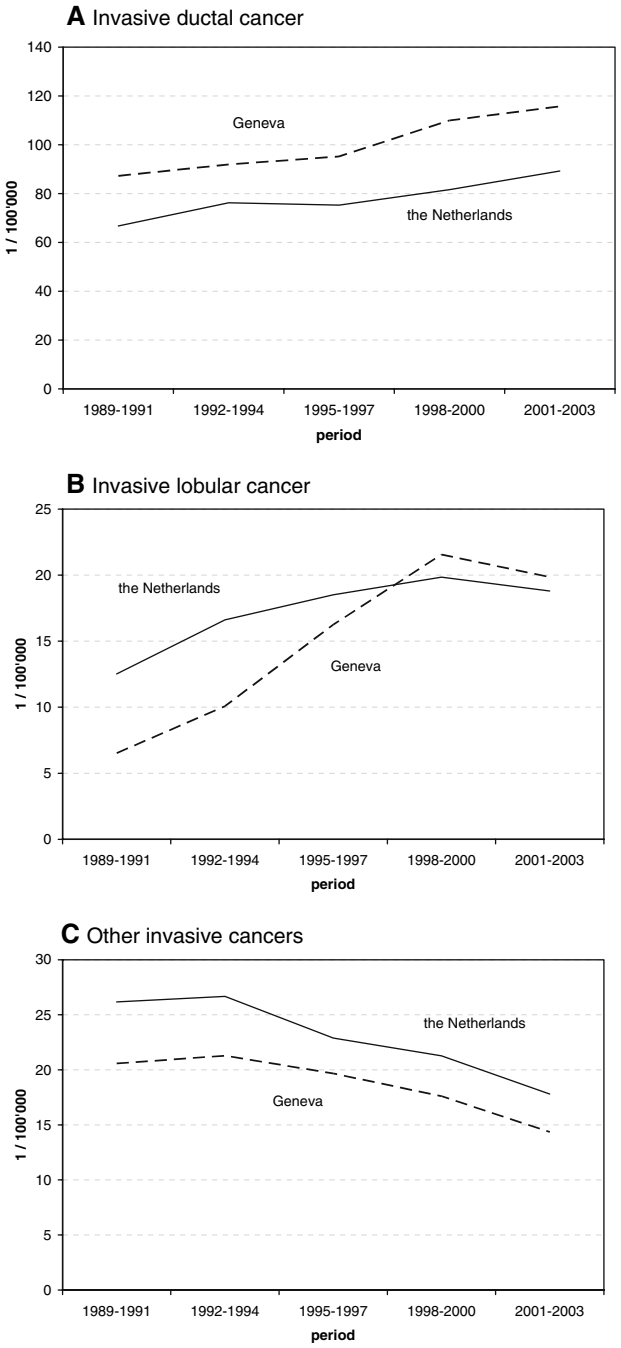

Fig. 3 Breast cancer incidence rates according to histological subtype. The Netherlands and Geneva, Switzerland, 1989–2003

cancer, simply because this change did not occur in the intensively screened population of the Netherlands.

This is supported by a recent study from Denmark, which reported a similar change in age-incidence rates among women who did not participate in the screening program (80% of the Danish female population) [11]. Since opportunistic screening also is uncommon in Denmark, again, the change could simply not be attributed to mammography screening.

Some studies evoked HRT as an explanation for the shift in age-specific breast cancer rates. A study from Norway among 45–60 year old women showed that, compared to women who did not use HRT or mammography screening, those who underwent screening mammography had a 20% increased risk of having breast cancer diagnosed [28]. However, women who did not use mammography screening, but who were current users of HRT had a more than doubled risk of being diagnosed with breast cancer.

In a previous study from Geneva, we demonstrated that the changed incidence pattern, i.e. incidence 'peak' among middle-aged women and deficit of breast cancer cases among elderly women, was only present among women who reported ever use of HRT, regardless whether their tumor was screen detected or not [9].

We realize that the shift in age-incidence rates of breast cancer is major and the association between living in Geneva and using HRT must be very strong for it to explain the changes observed. However, HRT use in Geneva is particularly prevalent. The proportion of current HRT users among women aged 45–59 years increased from 34% in 1993 to over 50% in 1996 [24]. More recently, Morabia and Constanza [25] showed that in the first six months of 2002 46% of all women between 35 and 74 years were current users of HRT. On average women started using HRT at 51 years and continued their use for a rather long duration (7.8 years on average). It is therefore quite likely that the proportion of current users among women aged 45–59 years would have been much higher. In contrast, the prevalence of HRT use is low in the Netherlands, only 13–19% of middle-aged Dutch women were current users of HRT during the nineties and the median duration of use was 2 years [23].

The sharp contrast in prevalence and duration of HRT use between the Netherlands and Geneva could be a valid explanation for the changes in breast cancer incidence and age distribution between the two populations.

In fact, HRT may not only explain the shift in age-incidence, but also the disproportionate increase in lobular cancer incidence, since many case-control and cohort studies have demonstrated strong links between HRT and lobular histology and, to a lesser extent, ductal cancer [18, 19, 30]. Li et al. examined the relation between HRT and lobular breast cancer and reported a significantly increased risk of lobular cancer (Odds Ratio [OR] 2.6) but not of ductal cancer (OR 0.7) among current users of combined HRT (including oestrogen and progesterone) [29]. Tjonneland et al. [20] prospectively investigated the breast cancer occurrence in a cohort of 29,875 women and found an increased risk of lobular breast cancer (Hazard Ratio [HR] 3.5) and ductal breast cancer (HR 2.1) among women using combined HRT. Especially long-term duration of HRT is associated with an increased risk of invasive lobular cancer.

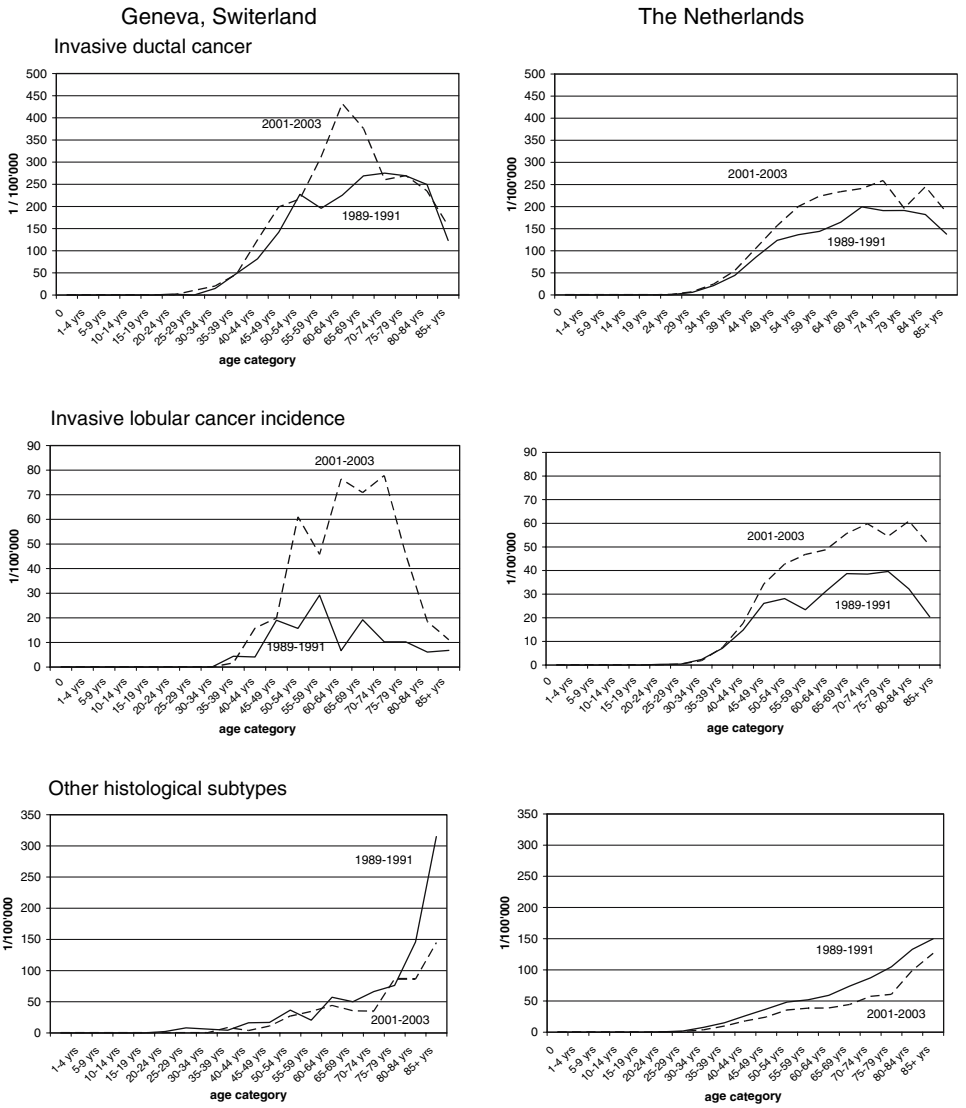

Fig. 4 Evolution of breast cancer incidence according to histological subtype and age. Geneva Switzerland and the Netherlands

Other potential explanations for the disproportionate increase in lobular cancer in Geneva include increased diagnostic activity, improvement in diagnostic techniques, and changes in diagnostic criteria. In the late 1970s the definition of invasive lobular carcinoma was broadened after new histologic variants were defined [30, 31]. However, since then, no major shifts in histological definitions have taken place. We consider it therefore unlikely that changes in broadening of histological criteria explain the differences in histological subtyping between the two populations occurring during the nineties.

Despite the fact that the sizes of the two study populations are very different, we are confident of the validity of our results. In fact, both groups are well defined populations, derived from two very reliable population-based cancer registries, and even the smaller population of Geneva still provided a large number of patients.

Nevertheless, we realize that our ecological study cannot provide conclusive evidence as to what has caused the shift in age distribution in breast cancer incidence in Geneva. Nevertheless, we would like to conclude that the absence of the shift in age-specific breast cancer rates in the Netherlands, a country with a long tradition and high level of implementation of mammography screening, renders screening a very unlikely explanation for the incidence changes seen in many European and North American populations. Given the important difference in HRT use during the 1990s between the Dutch and the Geneva populations, it becomes increasingly likely that HRT could be a key factor in the change in age distribution of breast cancer. However, other etiological factors cannot be excluded to have contributed to the shift in age distribution of breast cancer.

Acknowledgements Dr. H. M.Verkooijen was financially supported by a PROSPER Grant (3233-069350) from the Swiss National Science Foundation.

References

1. Ravdin PA, Cronin KA, Howlander N et al (2006) A sharp decrease in breast cancer incidence in the United States in 2003. Breast Cancer Res Treatm 100:S6–S7
2. Gøtzsche PC, Olsen O (2000) Is screening for breast cancer with mammography justifiable? Lancet 355:129–134
3. Olsen O, Gøtzsche PC (2001) Systematic review of screening for breast cancer with mammography. The Lancet Publishing Group, London, UK
4. Writing Group for the Women's Health Initiative Investigators (2002) Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. JAMA 288:321–333
5. Beral V, Million Women Study Collaborators 2003 Breast cancer and hormone-replacement therapy in the Million Women Study. Lancet 362:419–427
6. Jonsson H, Johansson R, Lenner P (2005) Increased incidence of invasive breast cancer after the introduction of service screening with mammography in Sweden. Int J Cancer 117:842–847
7. Zahl PH, Strand BH, Maehlen J (2004) Incidence of breast cancer in Norway and Sweden during introduction of nationwide screening: prospective cohort study. BMJ 328:921–924
8. Otto SJ, Fracheboud J, Looman CW et al (2003) Initiation of population-based mammography screening in Dutch municipalities and effect on breast-cancer mortality: a systematic review. Lancet 361:1411–1417
9. Bouchardy C, Morabia A, Verkooijen HM et al (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 6:78
10. Prehn A, Clarke C, Topol B et al (2002) Increase in breast cancer incidence in middle-aged women during the 1990s. Ann Epidemiol 12:476–481
11. Fuglede N, Langballe O, Svendsen AL et al (2006) Development in incidence of breast cancer in non-screened danish women, 1973–2002–a population-based study. Int J Cancer 118:2366–2369
12. Hemminki K, Rawal R, Bermejo JL (2004) Mammographic screening is dramatically changing age-incidence data for breast cancer. J Clin Oncol 22:4652–4653
13. Hemminki K, Bermejo JL (2005) Effects of screening for breast cancer on its age-incidence relationships and familial risk. Int J Cancer 117:145–149
14. Li CI, Anderson BO, Porter P et al (2000) Changing incidence rate of invasive lobular breast carcinoma among older women. Cancer 88:2561–2569
15. Verkooijen HM, Fioretta G, Vlastos G et al (2003) Important increase of invasive lobular breast cancer incidence in Geneva, Switzerland. Int J Cancer 104:778–781
16. Levi F, Te VC, Randimbison L et al (2003) Increase in lobular breast cancer incidence in Switzerland. Int J Cancer 107:164–165
17. Li CI, Anderson BO, Daling JR et al. (2003) Trends in incidence rates of invasive lobular and ductal breast carcinoma. JAMA 289:1421–1424
18. Li CI, Malone KE, Porter PL et al (2003) Relationship between long durations and different regimens of hormone therapy and risk of breast cancer. JAMA 289:3254–3263
19. Daling JR, Malone KE, Doody DR et al (2002) Relation of regimens of combined hormone replacement therapy to lobular, ductal, and other histologic types of breast carcinoma. Cancer 95:2455–2464
20. Tjonneland A, Christensen J, Thomsen BL et al (2004) Hormone replacement therapy in relation to breast carcinoma incidence rate ratios: a prospective Danish cohort study. Cancer 100:2328–2337
21. Bouchardy C (1997) Switzerland, Geneva. In: Parkin DM, Whelan SL, Ferlay J, Raymond L, Young J (eds) Cancer incidence in five continents. Vol. VII. International Agency for Research on Cancer, Lyon
22. Chamot E, Charvet AI, Perneger TV (2007) Who gets screened, and where: a comparison of organised and opportunistic mammography screening in Geneva, Switzerland. Eur J Cancer 43:576–584
23. van Duijnhoven FJ, Van Gils CH, Bezemer ID et al (2006) Use of hormones in the menopausal transition period in the Netherlands between 1993 and 1997. Maturitas 53:462–475
24. Schaad MA, Bonjour JP, Rizzoli R (2000) Evaluation of hormone replacement therapy use by the sales figures. Maturitas 34:185–191
25. Morabia A, Costanza MC (2006) Recent reversal of trends in hormone therapy use in a European population. Menopause 13:111–115
26. World Health Organization (1976) ICD-O International classification of diseases for oncology. Geneva
27. GLIM 4 the statistical system for generalized linear interactive modelling [computer program]. (1993) Oxford University Press, Oxford
28. Bakken K, Lund E, Eggen AE (2005) The impact of hormone replacement therapy on the incidence of breast cancer in Norway. J Clin Oncol 23:3636–3637
29. Li CI, Weiss NS, Stanford JL et al (2000) Hormone replacement therapy in relation to risk of lobular and ductal breast carcinoma in middle-aged women. Cancer 88:2570–2577
30. Martinez V, Azzopardi JG (1979) Invasive lobular carcinoma of the breast: incidence and variants. Histopathology 3:467–488
31. Fechner RE (1975) Histologic variants of infiltrating lobular carcinoma of the breast. Hum Pathol 6:373–378