PERGAMON

European Journal of Cancer 39 (2003) 1738–1745

European Journal of Cancer

www.ejconline.com

Does hormone replacement therapy increase the frequency of breast atypical hyperplasia in postmenopausal women? Results from the Bouches du Rhone district screening campaign

A. Gayet[a], J. Estève[a], B. Séradour[b], L. Piana[b], J. Jacquemier[c,d,*]

[a]*Service de Biostatistiques, Centre Hospitalier Lyon Sud, Bât 1M, 165 Chemin du Grand Revoyer, 69495 Pierre Bénite, France*
[b]*ARCADES (Association pour la Recherche et le Dépistage des Cancers du sein), Hôpital La Timone, Bâtiment F, Rue Saint Pierre, 13385 Marseille cedex 5, France*
[c]*Institut Paoli Calmettes, Service d'Anatomie pathologique, 232 Boulevard Sainte Marguerite, 13009 Marseille, France*
[d]*Association des Pathologistes du Sud (APSUD), France*

Received 27 June 2002; received in revised form 16 September 2002; accepted 10 December 2002

Abstract

It is thought that the risk of atypical hyperplasia (AH) increases with age, particularly among postmenopausal women. Three hypotheses were investigated to try to explain this phenomena: use of hormone replacement therapy (HRT), increased breast cancer screening and improvements in radiological quality. Data were collected from the Bouches du Rhône breast cancer screening programme database and from the pathological registry of all women operated on for breast diseases in the district. The AH incidence rate was studied using a Poisson regression analysis. The change in the profile of breast diseases was explored through studying changes in the proportion of AH among benign lesions and malignant diseases. The AH incidence rate significantly increased over time (13.6% per year). The proportion of AH among the benign diseases increased with time and was significantly higher for HRT users (Odds Ratio (OR) = 2.05; 95% Confidence Interval (CI): 1.43–2.93). While AH decreased with age among HRT non-users, it increased among users as a proportion of both benign and malignant lesions. The AH incidence rate significantly increased among pre- and postmenopausal women. Our study suggests that this increase is partly explained by the incidental discovery of these lesions by mammography and partly by a real increase of the disease among HRT users.

Keywords: Atypical hyperplasia; Hormone replacement therapy; Screening programme for breast cancer; Improvements in radiological quality; Training of radiologists; Reading mammograms

1. Introduction

Atypical hyperplasia (AH) (atypical lobular and/or ductal hyperplasia) is a benign breast disease which has been reported as a high risk factor for breast cancer [1–3]. In a retrospective cohort study, Dupont and Page [1] demonstrated that women with AH, aged less than 50 years, had a 4- to 5-fold increase in breast cancer risk compared with women of a similar age from the general population. A histological model of human breast cancer showed that AH naturally evolves to *in situ* carcinomas (CIS) then to invasive carcinomas and metastatic disease [4]. In premenopausal women, AH is influenced by sex hormones [5–7]. In fact, oestrogens, mediated through the oestrogen receptors, play a central role in regulating the growth and differentiation of the normal breast by stimulating and regulating the progesterone receptors that itself mediates the mitogenic effects of progesterone [8]. In postmenopausal women, the proportion of oestrogen receptors is stable in the absence of hormone replacement therapy (HRT) [9]. It is thought that AH increases over time in postmenopausal women, but this has not yet been documented. Three factors may explain the changes in the pattern of the AH trend among postmenopausal women. Firstly, HRT has been widely prescribed to postmenopausal women in order to reduce the side-effects of menopause [10] and as a possible means of reducing the risk of osteoporosis and

* Corresponding author. Tel. +33-4-9122-3457; fax: +33-4-9122-3573.
E-mail address: jacquemierj@marseille.fnclcc.fr (J. Jacquemier).

0959-8049/03/$ - see front matter © 2003 Published by Elsevier Ltd.
doi:10.1016/S0959-8049(02)00837-7

cardiovascular diseases [11]. Secondly, screening programmes for breast cancer have been extended in most of the French districts leading to increased incidental discovery of the disease. Finally, radiological quality has been improved in the 1990s.

The aim of this study was to quantify the AH incidence time trend in the Bouches du Rhône district and to examine the contribution of screening and HRT to the observed time change.

2. Materials and methods

2.1. Study design

2.1.1. Subjects

We carried out a retrospective study based on two information sources. Firstly, the screening programme for breast cancer from the Bouches du Rhône district, called ARCADES (Association pour la Recherche et le DEpistage des CAncers du Sein), which started in 1990. The target population consisted of all women aged 50–69 years who are invited every 3 years to attend screening by single oblique view mammograms. Breast lesions detected at screening were followed-up at the coordinating centre, by contacting the patient or her general practitioner [12]. Secondly, a pathological registry (Association des Pathologistes de Sud (APSUD)) of all breast lesions operated upon in the district including women of all ages, was set up at the start of the screening programme. Initial categorisation of the histological diagnosis was based on the World Health Organization (WHO) classification of breast diseases. Pathological data were actively retrieved in the APSUD database by a standardised form, according to European recommendations. The two sources of data were merged into a database containing 25 548 breast diseases. We restricted our analysis to women aged 40–69 years and to the years 1990–1999 for the incidence study ($n = 15\ 643$) then to 1994–1999 for the study of AH proportion according to HRT use from 1994 ($n = 8890$). HRT data were only available from 1994 onwards.

The variables used in the analysis were: calendar year, breast lesion histology, age at biopsy, HRT use, reasons for performing a breast biopsy and existence of a past mammogram. HRT use was collected from 1994 onwards for the screening programme participants as 'ever/never users'. The existence of past mammographic exams before entering the screening programme was also available for the screening programme participants (Table 1).

2.1.2. Population

The French National Statistical Institute for Economic Studies (INSEE) provided the Bouches du Rhône population numbers divided according to 5-year age groups, gender and calendar year (from 1990 to 1999).

The National Health Insurance for the Bouches du Rhône district provided the numbers of mammograms performed during the years 1995 and 2000 within the organised screening programme and outside of it. In the latter, mammography was prescribed for diagnostic and screening purposes with no possibility of differentiating between them.

2.2. Methods

2.2.1. Definition of pathological groupings

Five pathological groups have been defined [1,13]: non-proliferative diseases (NP), proliferative disease without atypia (PDWA), atypical hyperplasia, including mainly ductal and or lobular (AH), carcinoma *in situ* (CIS) and invasive carcinoma. NP, PDWA and AH are defined as benign breast diseases. CIS and invasive carcinoma are defined as malignant breast lesions [13].

The database does not include malignant phyllode diseases; benign phyllode diseases have been classified in the PDWA group.

Quality control meetings were organised for the Bouches du Rhône pathologists in order to improve the application of the European guidelines on the histological classifications [14,15].

2.2.2. Statistical analyses

Statistical analysis was performed using Poisson regression [16] to explore the changes in incidence rates of benign breast diseases and malignant breast lesions from 1990 to 1999. In order to study the influence of HRT, screening programme and radiological quality on the proportion of AH, logistic regression [17] was used. Logistic regression provided maximum likelihood estimates of the Odds Ratios (OR) and its Confidence Intervals (95% CI). Interaction was tested at the 10% level. Nested models were compared using likelihood ratio tests. When the calendar year was included as a continuous variable, 1996 was taken as the reference year. Association between the categorical variables was assessed with the Chi-square test [18]. P values less than 5% were considered significant.

In order to study the influence of HRT use on the distribution of benign lesions, we had to classify all women in a contingency table with calendar year, age and HRT use as a classification axis in addition to the type of lesions. This was done by considering that all women under 50 years were non-users and that non-participants in the screening programme were users in the same proportions as the participants for each calendar year×age cells.

Table 1
Description of the characteristics of the patients recorded in the registry between 1994 and 1999 and restricted to 40–69 year old women

	Benign histology			Malignant histology	
	NP	PDWA	AH	CIS	Invasive carcinoma
Lesion numbers restricted to women aged 40–69 years ($n=8890$)	1919	1928	263	449	4331
Mean age at the screening programme	59.47±0.6	59.18±0.6	59.59±2.1	60.01±1.1	61.00±0.32
Mean age at biopsy					
Screening programme participants	60.32±0.6	59.95±0.6	60.31±2.2	60.75±1.1	61.82±0.3
Screening programme non-participants	51.19±0	49.24±0.3	51.1±0.9	53.5±0.8	54.11±0.3
HRT information in women aged 50–69 years ($n=1\,598$)	306	257	29	95	911
No ($n=1\,209$)	232	190	17	68	702
Yes ($n=347$)	63	62	12	25	185
Missing values ($n=42$)	11	5	0	2	24
Mammography before the programme in 50–69 year olds ($n=1594$)	306	257	29	95	907
No ($n=676$)	120	114	10	35	397
Yes ($n=918$)	186	143	19	60	510

HRT, hormone replacement therapy; CIS, carcinoma *in situ*; AH atypical hyperplasia; NP, non-proliferative diseases; PDWA, proliferative disease without atypia.

3. Results

3.1. AH incidence rate

After an initial increase due to the diagnosis of prevalent cases, the incidence rate of total breast benign diseases (NP, PDWA and AH) decreased almost linearly between 1994 and 1999 (Fig. 1). The incidence rate of benign breast lesions varied from 230.67 per 100 000 person-years to 196.27 per 100 000 person-years between 1994 and 1999 (rate of change of −3.8% per year (−1.9 to −5.6%)) in women aged 40–69 years (Fig. 1). In contrast, the incidence rate of AH varied from 11.42 to 18.59 per 100 000 person-years over the same period (rate of increase of +13.6% per year (+6.4 to +20.9%)) (Fig. 2). The incidence rate of malignant breast diseases increased from 205.66 to 283.05 per 100 000 person-years (rate of increase of 6.9% per year (+5.3 to +8.6%)) between 1994 and 1999 in women aged 40–69 years (Fig. 1). Invasive carcinoma increased at +5.9% per year (+4.2 to 7.7%), between 1994 and 1999, while CIS increased much more steeply at +17.1% per year (+11.6 to +22.7%) during the same period (Fig. 2). The rates of change both for benign and for malignant lesions are the same in the three age groups (no calendar year by age interaction: $\chi^2=0.48$ on 2 degrees of freedom (df)). In particular, the increase of AH is not greater among women aged less than 50 years than among older women.

3.2. The influence of HRT use on the proportion of the AH among benign breast diseases and malignant breast lesions

3.2.1. AH proportion among benign breast diseases

The probability of observing AH, among other benign breast diseases (NP and PDWA), increased significantly between 1994 and 1999 (OR = 1.20, $P<0.001$) (model 1 in Table 2).

The trend for the proportion of AH among benign breast diseases was not modified, after adjustment for the confounding variables, age at biopsy and screening programme participation. The AH proportion increased significantly with age (trend test: $P=0.049$). The proportion of AH was lower among screening programme participants than among non-participants (OR = 0.63, $P=0.037$) (model 2 in Table 2).

The AH proportion was significantly higher in HRT users compared with HRT non-users (OR = 2.05, $P<0.001$) (model 3 in Table 2). When HRT use was taken into account, the influence of age on the proportion of AH disappeared suggesting that this effect was due to postmenopausal treatment. This was confirmed by the estimation of the age×HRT interaction showing that this increase was limited to HRT users (model 4 in Table 2).

3.2.2. The proportion of AH among malignant breast lesions

Grouping AH with the malignant lesions, the proportion of AH showed a non-significant increase with calendar year (model 1 in Table 3). The AH proportion decreased significantly with age and was lower among screening programme participants (model 2 in Table 3).

The AH proportion was significantly higher among HRT users (OR = 1.77, $P=0.002$) (models 3 and 4 in Table 3). After adjustment for HRT use, the proportion of AH decreased steeply with age among non-users of HRT, while it increased among users.

3.3. Increased screening for breast cancer

The numbers of mammograms performed in 1995 and in 2000 within the ARCADES programme and outside

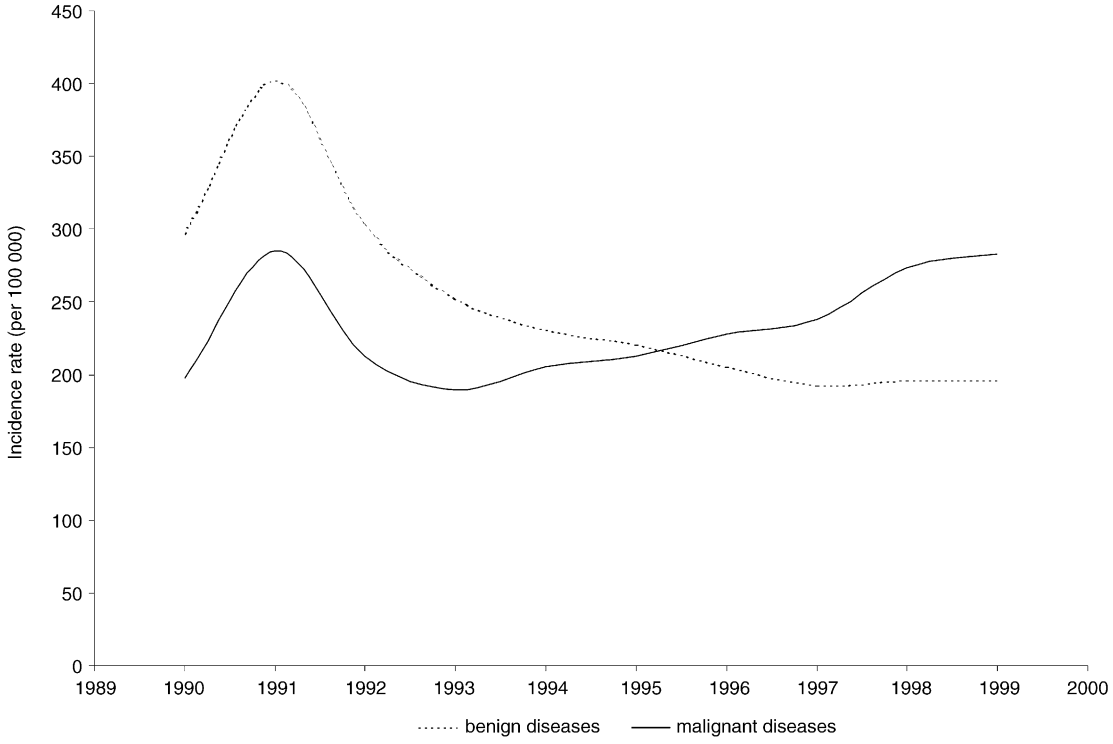

Fig. 1. Time trend of distribution of benign lesions and malignant lesions in women aged 40–69 (time period 1990–1999).

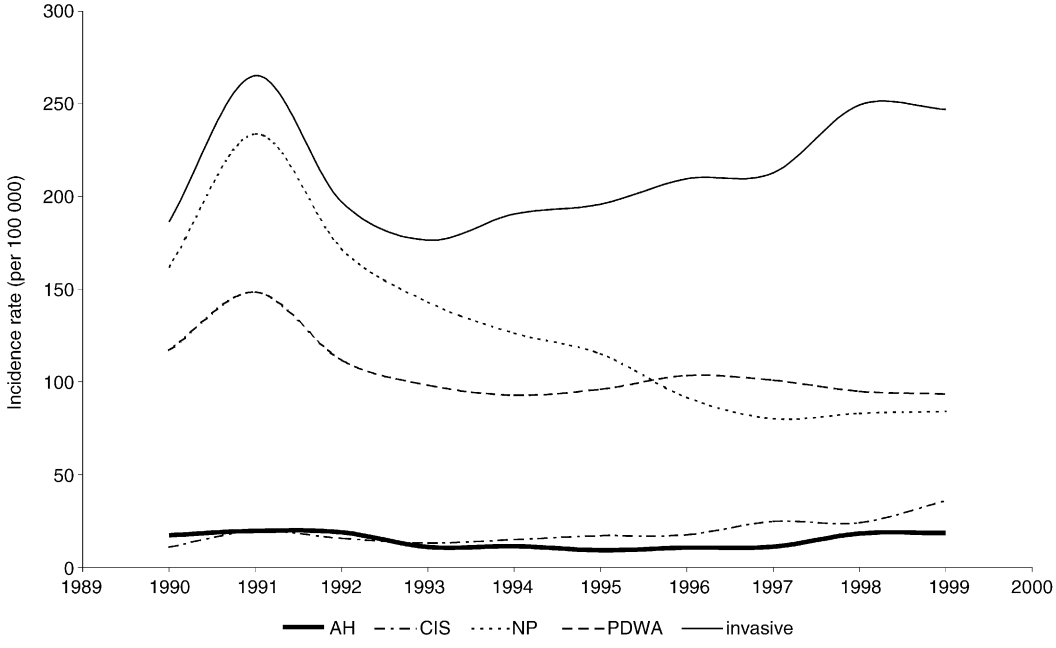

Fig. 2. Time trends for pathological groups in women aged 40–69 years (time period 1990–1999).

of it were 38 689 and 65 112, respectively. These figures correspond to an increase in the proportion of women having a mammogram from 26 to 34%. In 1995, the proportion was made up of 15% participating in the ARCADES programme and 11% outside of it. In 2000, these proportions were 14 and 20%, respectively. In the ARCADES programme, HRT users were more likely than non-users to have already undergone a mammographic exam before entering the screening programme. This association was observed among women aged 50–59 years and 60–69 years. The summary OR was 5.05 (95% CI: 3.69–6.92).

These two observations are not by themselves proof that mammograms performed outside of the organised screening programme are responsible for the AH excess among HRT users. Comparing, among HRT non-users,

Table 2
Time trends for the proportion of AH among benign breast diseases (logistic regression)

Model variables			OR (95% CI)	*P* value
Model 1	Calendar year:		1.20 (1.11–1.29)	$<10^{-3}$
Model 2	Calendar year:		1.19 (1.11–1.29)	$<10^{-3}$
	Age (years):	40–49	1 (1.11–1.29)	$<10^{-3}$
		50–59	1.27 (0.95–1.69)	1.104
		60–69	1.39 (0.97–2.00)	0.074
	Screening programme participation:	No	1	
		Yes	0.63 (0.41–0.97)	0.037
Model 3	Calendar year:	1994–1996	1	
		1997–1999	1.83 (1.40–2.39)	$<10^{-3}$
	Age (years):	40–49	1	
		50–59	0.83 (0.59–1.16)	0.276
		60–69	0.88 (0.61–1.27)	0.499
	HRT use:	No	1	
		Yes	2.05 (1.43–2.93)	$<10^{-3}$
Model 4	Calendar year:		1.21 (1.12–1.31)	$<10^{-3}$
	Age (years)×HRT	40–49×No	1	
		50–59×No	1.00 (0.72–1.39)	0.989
		60–69×No	0.66 (0.42–1.04)	0.075
		50–59×Yes	1.33 (0.86–2.06)	0.203
		60–69×Yes	3.39 (1.60–7.18)	0.001

OR, Odds Ratio; 95% CI, 95% Confidence Interval.

Table 3
Time trends for the proportion of AH among malignant breast lesions (logistic regression)

Model variables			OR (95% CI)	*P* value
Model 1	Calendar year:		1.07 (0.99–1.15)	0.064
Model 2	Calendar year:		1.06 (0.98–1.14)	0.145
		40–49	1	
	Age: (years)	50–59	0.76 (0.57–1.02)	0.066
		60–69	0.41 (0.29–0.59)	$<10^{-3}$
	Screening programme participation:	No	1	
		Yes	0.66 (0.44–1.01)	0.057
Model 3	Calendar year:	1994–1996	1	
		1997–1999	1.26 (0.97–1.64)	0.087
	Age (years):	40–49	1	
		50–59	0.50 (0.36–0.70)	$<10^{-3}$
		60–69	0.28 (0.19–0.39)	$<10^{-3}$
	HRT use:	No	1	
		Yes	1.77 (1.24–2.52)	0.002
Model 4	Calendar year:		1.06 (0.98–1.15)	0.133
	Age (years)×HRT	40–49×No	1	
		50–59×No	0.64 (0.46–0.89)	0.008
		60–69×No	0.18 (0.11–0.28)	$<10^{-3}$
		50–59×Yes	1.03 (0.67–1.58)	0.894
		60–69×Yes	5.58 (3.08–10.1)	$<10^{-3}$

Table 4
AH proportion among benign breast diseases and malignant breast lesions in screening programme participants and non-HRT users only (logistic regression) and past mammography impact

Model variables		OR (95% CI)	*P* value
AH proportion among benign breast disease			
Calendar year:		1.38 (1.00–1.89)	0.049
Age (years):	50–59	1	
	60–69	1.20 (0.44–3.25)	0.720
Past mammography:	No	1	
	Yes	1.02 (0.38–2.74)	0.961
AH proportion among malignant breast lesions			
Calendar year:		1.25 (0.92–1.69)	0.150
Age (years):	50–59	1	
	60–69	0.54 (0.19–1.48)	0.229
Past mammography:	No	1	
	Yes	0.94 (0.35–2.58)	0.912

the AH proportion between those who had and those who did not have a test before entering the programme, did not show any significant difference (Table 4).

4. Discussion

To our knowledge, this retrospective study is the first one evaluating the AH incidence pattern over time among postmenopausal women.

The main result of our study is that, among 40–69 year old women, the AH incidence rate significantly increased over time (13.6% per year from 1994 to 1999) in the Bouches du Rhône district, while the other benign breast diseases steadily decreased. Moreover this increase was still present among postmenopausal women (15.4% per year from 1994 to 1999), and the rate of increase of the incidence of AH is significantly greater than that of the incidence of malignant disease among 40–69 year old patients, whatever their age at diagnosis.

Due to the fact that AH is a well characterised pre-malignant lesion, it may be rewarding to investigate the possible causes of this increasing incidence rate. The first possible explanation for the increasing incidence rate of AH is due to changes in the epidemiological context. To explore this, we studied the AH proportion among benign breast diseases and among malignant breast lesions, according to the calendar year, age and HRT use. The AH proportion among benign breast diseases significantly increased in women aged 40–69 years, between 1994 and 1999, while the proportion of AH was only slightly modified among malignant breast lesions. Benign breast disease other than AH decreased continuously over time, while AH and CIS increased more steeply than invasive carcinomas. The AH proportion among malignant breast lesions was significantly lower in

older women compared with the 40–49 age-group, due to the fact that malignant breast lesions are more common in postmenopausal women. In this study, the AH proportion among benign breast diseases was higher in women outside of the screening programme ($P = 0.037$) and it was also marginally higher for the malignant lesions ($P = 0.057$). This could be partially explained by the fact that the criteria to perform a breast biopsy were different for screening programme participants and those outside of it. In the screening programme, specificity is of primary concern with the need to reduce false-positive cases, whereas outside of the programme, the focus is on sensitivity in order to avoid false-negatives [25].

The AH proportion among benign breast diseases and among malignant breast lesions were both significantly higher in the HRT users groups. A previous study [26] demonstrated such a tendency in a series of 156 benign breast biopsies from postmenopausal women treated or not with HRT. The proportion of patients with AH was 15% for the HRT users and only 4% for the non-users. Our study strongly suggests that HRT prevents a decrease in AH after menopause.

The oestrogen receptor (ERα) level increases significantly during menopause [27]. Experimental studies [28] have demonstrated in a MCF7 10AT xenograft model that 17β oestradiol implants drive to different stages of carcinogenesis (AH then CIS and invasive carcinoma) for 92% of cases after 10 weeks of exposition. Authors have suggested two different pathways of mammary carcinogenesis, oestrogen-dependent and oestrogen-independent [27,29]. In a previous study, we demonstrated an increasing frequency of breast carcinoma among HRT users [25]. Case–control studies provided some evidence of an additional effect of progestin on the breast cancer risk in oestro-progestative HRT [30]. Another case control study demonstrated that women with AH had an increased risk of invasive carcinoma [13]. However, this was not further increased by HRT use [31]. Studies investigating genetic changes have highlighted the fact that AH and invasive lesions had a similar loss of heterozygosity on chromosomes 16q and 17p [32]. All of these studies have provided wide ranging arguments to explain the mechanism of the increase in the AH incidence rate and subsequent progression to oestrogen-dependent invasive lesions [33]. The type of drugs, dosage routine, frequency of administration and duration are unfortunately not available in our database, but we could suppose that 60–69 years old HRT users, were treated at an early age.

A weakness of our study is the lack of information on HRT use among non-participants in the ARCADES programme. We used a rough method for imputation of missing values in our statistical analysis with the objective of contrasting the AH incidence in premenopausal women with that in postmenopausal women. It is likely that among the 60–69 year old women, the proportion of HRT users is larger among non-participants, who are more often followed by gynaecologists, than among participants, where 90% are followed by a general practitioner. However, according to the figures we had available, we could assume that HRT consumption among ARCADES participants reflects HRT use in the general population. In 1998, in a survey by the pharmaceutical industry, the prevalence of HRT use was approximately 30% among women aged 50–64 years, while it was 27% among ARCADES participants of the same age. When studying the effect of HRT in a complete case analysis, that is essentially among screening programme participants, the AH proportion is still significantly greater in HRT users (OR = 2.51, 95% CI: 1.14–5.49 to 2.62, 95% CI: 1.18–5.83, respectively if the denominator is benign diseases to malignant lesions, respectively.

In the 1990s, radiological quality has continuously improved [19,20] and this could explain the decline in the incidence rate of benign breast diseases due to the performance of fewer useless biopsies (higher specificity of mammography) [20–22]. Generally, AH are diagnosed on radiological microcalcifications, as is the CIS subtype [23]. The way to differentiate these two diagnoses is with the use of high-quality enlargement of screening mammography. This might explain the simultaneous rise in the AH and CIS incidence rates, which were incidentally detected following the discovery of microcalcification on screening mammography. The availability of needle core biopsy as an alternative to systematic surgical excision could be an explanation for the more frequent explorations of radiological microcalcifications. Surgical excision is only performed if AH is diagnosed on core biopsy [24]. This technique could be a valuable alternative to abusive open biopsy and could lead to an increase in the number of true benign lesions, especially AH. However, this practice has been developed too recently in the Bouches du Rhône district to explain the rise in the AH incidence rate.

Thirdly, the increase in breast cancer screening among postmenopausal women could contribute to the rise in the AH incidence rate. Our data suggested that the medical surveillance of HRT users were more intensive than for non-users, which could be readily understood since HRT users are generally followed by gynaecologists who are more prone to prescribe screening mammograms together with any postmenopausal treatment. Our study emphasised changes in breast cancer screening practices. The proportion of 50–69 year old women who had a mammography in 2000 was significantly greater than in 1995. This increase was mainly due to examinations performed outside of the screening programme. It is, however, difficult to assess the contribution of this change in mammogram frequency to the increase of AH incidence. While it is true that AH is less often detected among ARCADES participants, it is not more often detected among participants who had a tendency to be tested also outside of the programme.

5. Conclusions

The study clearly demonstrated that the AH incidence rate increased between 1994 and 1999, while other benign breast diseases globally decreased. AH proportion among other benign breast diseases also increased over time in women aged 40–69 years and this was significantly higher among HRT users, leading to the conclusion that HRT use might increase the development of AH. These results occurred in the context of a lower participation of postmenopausal women in the organised screening programme for breast cancer and in the context of improvements in radiological quality, especially better training of radiologists in reading in mammograms.

We recommend a core biopsy be conducted in patients who are HRT users with recently detected microcalcifications. Furthermore, a diagnosis of AH should lead to a reconsideration of HRT use in these patients.

Acknowledgements

We are grateful to F. Morin for help with the manuscript and L. Remontet for the statistical approach. This work has been supported by ARCADES, Institut Paoli-Calmettes, Ligue Départementale des Bouches du Rhone contre le Cancer.

References

1. Dupont WD, Page DL. Risk factors for breast cancer in women with proliferative breast disease. *N Engl J Med* 1985, **312**, 146–151.
2. Dupont WD, Parl FF, Hartmann WH, *et al*. Breast cancer risk associated with proliferative breast disease and atypical hyperplasia. *Cancer* 1993, **71**, 1258–1265.
3. London SJ, Connolly JL, Schnitt SJ, Colditz GA. A prospective study of benign breast disease and the risk of breast cancer. *JAMA* 1992, **267**, 941–944.
4. Allred DC, Mohsin SK, Fuqua SA. Histological and biological evolution of human premalignant breast disease. *Endocr Relat Cancer* 2001, **8**, 47–61.
5. Olsson H, Jernstrom H, Alm P, *et al*. Proliferation of the breast epithelium in relation to menstrual cycle phase, hormonal use, and reproductive factors. *Breast Cancer Res Treat* 1996, **40**, 187–196.
6. Potten CS, Watson RJ, Williams GT, *et al*. The effect of age and menstrual cycle upon proliferative activity of the normal human breast. *Br J Cancer* 1988, **58**, 163–170.
7. Hofseth LJ, Raafat AM, Osuch JR, Pathak DR, Slomski CA, Haslam SZ. Hormone replacement therapy with estrogen or estrogen plus medroxyprogesterone acetate is associated with increased epithelial proliferation in the normal postmenopausal breast. *J Clin Endocrinol Metab* 1999, **84**, 4559–4565.
8. Pike MC, Spicer DV, Dahmoush L, Press MF. Estrogens, progestogens, normal breast cell proliferation, and breast cancer risk. *Epidemiol Rev* 1993, **15**, 17–35.
9. Fuqua SA, Wiltschke C, Zhang QX, Borg A, Castles CG, Friedricks WE, Hopp T, Hilsenbeck S, Mohsin SK, O'Connell P, Allred DC. A hypersensitive estrogen receptor-alpha mutation in premalignant breast lesions. *Cancer Res* 2000, **60**(15), 4026–4029.
10. Turpin G. [Role of hormone replacement therapy during menopause in the cardiovascular prevention]. *Ann Cardiol Angeiol (Paris)* 1994, **43**, 177–180.
11. Orcel P. Risk factors and prevention of postmenopausal osteoporosis. *Rev Prat* 1995, **45**, 1107–1113.
12. Jacquemier J, Assada M, Aubert H, *et al*. [Departmental compilation of histoprognostic data in senology. Apropos of campaign screening in Bouches-du-Rhone]. *Bull Cancer* 1992, **79**, 999–1008.
13. Byrne C, Connolly JL, Colditz GA, Schnitt SJ. Biopsy confirmed benign breast disease, postmenopausal use of exogenous female hormones, and breast carcinoma risk. *Cancer* 2000, **89**, 2046–2052.
14. European recommendations for quality assurance in the setting of mammographic screening for breast cancer. Report of pathologists of the working group "Breast Cancer Screening" of the European Union. *Ann Pathol* 1996, **16,** 315–333.
15. Sloane JP, Amendoeira I, Apostolikas N, *et al*. [Guidelines for pathology—supplement to European guidelines for quality assurance in mammography screening. Report by the Pathology Working Group of the European Community]. *Pathologe* 1997, **18**, 71–88.
16. Breslow NE, Day NE. Fitting models to continuous data. In Breslow NE, Day NE, eds. *Statistical Methods in Cancer Research, vol. 5. IARC Scientific Publications No. 82*. Geneva, IARC, 2001, 185–192.
17. Breslow NE, Day NE. Unconditional logistic regression for large strata. In Breslow NE, Day NE, eds. *Statistical Methods in Cancer Research, vol. 6. IARC Scientific Publications No. 32*. Geneva, IARC, 2001, 192–246.
18. Breslow NE, Day NE. Analysis of groupated data. In Breslow NE, Day NE, eds. *Statistical Methods in Cancer Research, vol. 4. IARC Scientific Publications No. 32*. Geneva, IARC, 2001, 147–150.
19. Maccia C, Renaud R, Castellano S, *et al*. Quality control in mammography: an initiative in France. *Br J Radiol* 1994, **67**, 371–383.
20. Suleiman OH, Spelic DC, McCrohan JL, Symonds GR, Houn F. Mammography in the 1990s: the United States and Canada. *Radiology* 1999, **210**, 345–351.
21. Young KC, Wallis MG, Ramsdale ML. Mammographic film density and detection of small breast cancers. *Clin Radiol* 1994, **49**, 461–465.
22. Young KC, Wallis MG, Blanks RG, Moss SM. Influence of number of views and mammographic film density on the detection of invasive cancers: results from the NHS Breast Screening Programme. *Br J Radiol* 1997, **70**, 482–488.
23. Johnson JM, Dalton RR, Wester SM, Landercasper J, Lambert PJ. Histological correlation of microcalcifications in breast biopsy specimens. *Arch Surg* 1999, **134**, 712–715.
24. Ely KA, Carter BA, Jensen RA, Simpson JF, Page DL. Core biopsy of the breast with atypical ductal hyperplasia: a probabilistic approach to reporting. *Am J Surg Pathol* 2001, **25**, 1017–1021.
25. Seradour B, Esteve J, Heid P, Jacquemier J. Hormone replacement therapy and screening mammography: analysis of the results in the Bouches du Rhone programme. *J Med Screen* 1999, **6**, 99–102.
26. Cahn MD, Tran T, Theur CP, Butler JA. Hormone replacement therapy and the risk of breast lesions that predispose to cancer. *Am Surg* 1997, **63**, 858–860.
27. Roger P, Daures JP, Maudelonde T, *et al*. Dissociated overexpression of cathepsin D and estrogen receptor alpha in preinvasive mammary tumors. *Hum Pathol* 2000, **31**, 593–600.
28. Shekhar MP, Nangia-Makker P, Wolman SR, Tait L, Heppner GH, Visscher DW. Direct action of estrogen on sequence of progression of human preneoplastic breast disease. *Am J Pathol* 1998, **152**, 1129–1132.

29. Nandi S, Guzman RC, Yang J. Hormones and mammary carcinogenesis in mice, rats, and humans: a unifying hypothesis. *Proc Natl Acad Sci USA* 1995, **92**, 3650–3657.
30. Ross RK, Paganini-Hill A, Wan PC, Pike MC. Effect of hormone replacement therapy on breast cancer risk: estrogen versus estrogen plus progestin. *J Natl Cancer Inst* 2000, **92**, 328–332.
31. Dupont WD, Page DL, Parl FF, *et al*. Estrogen replacement therapy in women with a history of proliferative breast disease. *Cancer* 1999, **85**, 1277–1283.
32. Lakhani SR, Collins N, Stratton MR, Sloane JP. Atypical ductal hyperplasia of the breast: clonal proliferation with loss of heterozygosity on chromosomes 16q and 17p. *J Clin Pathol* 1995, **48**, 611–615.
33. Esteve J, Séradour B, Jacquemier J, Remontet L. Does a better grade of tumour occurring in women under hormone replacement therapy compensate for their lower probability of detection by screening mammography? *J Med Screen* 2002, **9**, 70–73.