Rates of Atypical Ductal Hyperplasia Have Declined with Less Use of Postmenopausal Hormone Treatment: Findings from the Breast Cancer Surveillance Consortium

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Abstract

Aim: **To examine risk factors and rates of atypical ductal hyperplasia (ADH) with and without associated breast cancer over time and tumor characteristics of breast cancer with and without associated ADH in women previously screened with mammography.**

Methods: **Data on screening mammograms done between 1996 and 2005 were collected from mammography registries that participate in the Breast Cancer Surveillance Consortium. Associations between age, family history of breast cancer, postmenopausal hormone treatment (HT), and final pathology result (ADH or cancer with or without ADH in the same breast) were examined. Rates of different outcomes were calculated per exam year. Tumor characteristics of cancers with and without associated ADH were compared.**

Results: **A total of 2,453,483 screening mammograms were associated with 1,064 biopsies with ADH, 833 breast cancers with ADH, and 8,161 cancers with no ADH. Postmenopausal HT use decreased significantly from 35% to 11% during the study period. Rates of ADH decreased from a peak of 5.5/10,000 mammograms in 1999 to 2.4/10,000 in 2005. Rates of cancer with ADH decreased from a peak of 4.3/10,000 mammograms in 2003 to 3.3/10,000 in 2005. ADH and breast cancer were significantly associated with use of postmenopausal HT. Cancer associated with ADH was of lower grade and stage and more estrogen receptor positive than cancer with no ADH.**

Summary: **Postmenopausal HT is associated with an increased risk of ADH with or without cancer. Rates of ADH have decreased over the past decade, which may be partially explained by the significant reduction in use of postmenopausal HT.** (Cancer Epidemiol Biomarkers Prev 2009;18(11):2822–8)

Introduction

A diagnosis of atypical ductal hyperplasia (ADH) is associated with a 3- to 5-fold increased risk of subsequent development of breast cancer (1-3). Because ADH is associated with microcalcifications on mammography, it has been detected more often since screening mammography was introduced (2, 4). Patients with a diagnosis of ADH in one breast are at risk of developing breast cancer in both breasts, suggesting that ADH is an indicator of overall breast cancer risk (5, 6). Some consider ADH a precursor of certain breast cancers. Using molecular analysis, Simpson et al. (7) and Viacava et al. (8) have shown similarities between low-grade ductal carcinoma *in situ* (DCIS) and ADH, arguing that ADH is the precursor of well-differentiated DCIS and low-grade invasive cancer. High rates of associated ADH and low-grade DCIS have been found in low-grade tumors (tubular cancer, tubulolobular cancer, and invasive lobular cancer) (9). These lesions had similar genetic alterations (recurrent loss of 16q, gain of 1q) as well as expression of the estrogen receptor and similar nuclear and cytoplasmic features, leading to the hypothesis that ADH and low-grade DCIS may be precursors of some invasive cancers.

Incidence rates of breast cancer in the United States have changed over the past few decades, with increases attributed to the introduction and dissemination of screening mammography and recent decreases attributed to the decreased use of postmenopausal hormone treatment (HT) (10-12). We examined risk factors and rates of ADH over time in a screened population, using 10 years of data collected by the Breast Cancer Surveillance Consortium (BCSC). We examined tumor characteristics of breast cancer with and without associated ADH and rates of cancer with and without ADH over time.

Materials and Methods

We included data from five mammography registries that participate in the National Cancer Institute–funded BCSC: the Carolina Mammography Registry, Group

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Table 1. Characteristics of women in the study

	Year of screening mammogram			
	1996-1998, *n* (%)	1999-2002, *n* (%)	2003-2005, *n* (%)	Total, *n* (%)
Total	617,998	1,194,045	641,440	2,453,483
Age at mammography, y				
40-49	174,131 (28)	336,038 (28)	171,928 (27)	682,097 (28)
50-59	196,561 (32)	384,569 (32)	208,737 (33)	789,867 (32)
60-69	134,723 (22)	249,313 (21)	137,662 (21)	521,698 (21)
70-79	90,295 (15)	173,233 (15)	91,632 (14)	355,160 (14)
80+	22,288 (4)	50,892 (4)	31,481 (5)	104,661 (4)
Family history of breast cancer (14% missing)				
No	377,404 (85)	913,200 (87)	520,173 (85)	1,810,777 (86)
Yes	64,839 (15)	141,531 (13)	93,729 (15)	300,099 (14)
Menopausal status				
Pre	94,070 (18)	222,995 (21)	141,943 (24)	459,008 (22)
Peri	8,033 (2)	14,161 (1)	12,012 (2)	34,206 (2)
Post	415,304 (80)	804,644 (77)	426,650 (74)	1,646,598 (77)
HT use (10% missing)				
No	332,677 (65)	710,381 (66)	529,226 (86)	1,572,284 (72)
Yes	178,660 (35)	357,991 (34)	87,439 (14)	624,090 (28)
Time since last mammography, y (1.5% missing)				
<1	18,518 (3)	21,453 (2)	6,223 (1)	46,194 (2)
1	399,405 (67)	891,303 (75)	493,200 (77)	1,783,908 (74)
2	129,232 (22)	186,421 (16)	98,617 (15)	414,270 (17)
3	33,773 (6)	54,279 (5)	25,820 (4)	113,872 (5)
4-5	18,247 (3)	27,416 (2)	13,843 (2)	59,506 (2)

Health Cooperative in Washington, the New Hampshire Mammography Network, the New Mexico Mammography Project, and the Vermont Breast Cancer Surveillance System.[6] These registries collect information on mammography examinations done in their defined catchment areas. Each mammography registry annually links women in their registry to a state tumor registry or regional Surveillance Epidemiology and End Results program that collects population-based cancer data as well as pathology databases that collect information on both benign and malignant diagnoses. The BCSC Statistical Coordinating Center pooled and analyzed the data. Each mammography registry and the Statistical Coordinating Center have received Institutional Review Board approval for either active or passive consenting processes or a waiver of consent to enroll participants, link data, and perform analytic studies. All procedures comply with the Health Insurance Portability and Accountability Act, and all registries and the Statistical Coordinating Center have received a Federal Certificate of Confidentiality and other protection for the identities of women, physicians, and facilities studied by this research.

The study sample included screening mammography examinations done between January 1, 1996 and December 31, 2005 on women ages 40 years and older with a previous screening mammography within 5 years and no personal history of breast cancer or breast augmentation. A screening mammogram was defined as a bilateral mammogram that the interpreting radiologist indicated was for routine screening. To avoid misclassifying diagnostic examinations as screening examinations, we excluded examinations done within 9 months of a prior breast imaging examination. Mammography examinations that occurred after December 31, 2005 were not included to ensure at least 12 months for reporting cancers to tumor registries after the most recent mammography examination.

Demographic and breast health history information was obtained using a self-administered questionnaire that included questions about family history of breast cancer (first-degree relative), time since previous mammography, menopausal status, and current use of postmenopausal HT. A woman was classified as postmenopausal if she reported that her menstrual periods stopped because of natural causes, both her ovaries were removed, she was of age 55 y or older, or she currently used postmenopausal HT. A woman was classified as perimenopausal if she was unsure if her periods had stopped or her last menstrual period was 180 to 364 days prior. A woman was classified as premenopausal if she currently used oral contraceptives for birth control or had a period within the last 180 days. Otherwise, women with a hysterectomy with one or more ovaries intact [$n = 64,076$ (2.6%)], women who reported their periods stopped for "other reasons" [$n = 43,930$ (1.8%)], and those who reported 365 or more days since their last period with no other information [$n = 5,785$ (0.2%)] were classified as unknown menopausal status. Time since last mammography was classified as <1 year (9-11 months), 1 year (12-23 months), 2 year (24-35 months), 3 year (36-47 months), or 4 to 5 year (48-60 months).

Pathology data included pathology results for the first biopsy done within 1 year of the screening mammogram and for all biopsies within the 3 months after the first biopsy. Type of biopsy (core versus excision) and result were recorded. Fine-needle aspiration specimens were excluded. Final pathology results (including all biopsies and records from the cancer registries) were classified as ADH, cancer (DCIS or invasive cancer) with ADH in the same breast, or cancer (DCIS or invasive carcinoma) without ADH in the same breast. Cancers were classified according to their grade (grades 1 and 2 were considered low grade), American Joint Committee on Cancer 5th edition (13) stage at diagnosis, and receptor status (estrogen,

[6] http://breastscreening.cancer.gov

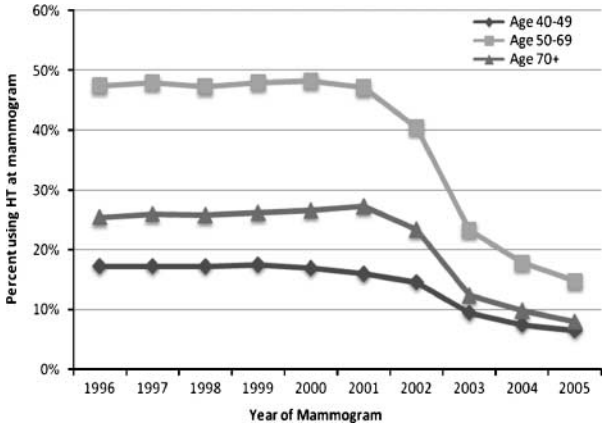

Figure 1. Rates of postmenopausal HT use per 10,000 screening mammograms, by age group, adjusted for age, time since last mammogram, and registry.

progesterone). Invasive cancers were classified according to their histology (ductal, lobular, mixed, and other).

Statistical Analysis. Characteristics of the women in the study, including age, family history, menopausal status, use of postmenopausal HT at time of mammogram, year of mammogram, and time since last mammogram, were summarized. We calculated the percentage of mammograms done in women using postmenopausal HT each year, by age group, adjusting to the mammography registry distribution of study population in 2000 using direct standardization. Unadjusted rates per 10,000 mammograms of pure ADH, ADH associated with cancer, and cancer with no ADH by patient characteristics were calculated. The association between patient characteristics and the outcomes (ADH, cancer with ADH, and cancer with no ADH) was assessed using logistic regression, adjusting for patient age (10-year age groups), family history of breast cancer, menopause status, postmenopausal HT use, time since last mammography, exam year, and mammography registry. Rates of pure ADH and cancer with and without associated ADH per 10,000 mammograms over time were estimated by age group, adjusting to the mammography registry, age, and time since last mammogram distribution of study population in 2000. Tumor characteristics of cancers with and without associated ADH were compared. Among women with cancer, we examined the probability of a favorable prognostic characteristic whether associated or not with ADH. Separate models were fit for each of the following cancer characteristics: DCIS versus invasive cancer, grade (low versus high) among DCIS cases and among invasive cancers, cancer histology (ductal versus other), stage (I versus II, III, or IV), estrogen receptor positive versus estrogen receptor negative, and progesterone receptor positive versus progesterone receptor negative.

Results

Data were available for 2,453,483 screening mammography examinations done on women with a screening mammogram within the previous 5 years. The mean age of the patients was 57.5 years and increased slightly during the study years (Table 1). Approximately 15% of the participants reported a family history of breast cancer; this rate was stable throughout the study. The use of postmenopausal HT decreased sharply from 35% in 1999-2000 to 11% in 2005; this decline was most pronounced in the 50- to 69-year age group (Fig. 1). After the completion of all imaging workup, 1.3% of mammograms were recommended for a biopsy. The use of core biopsy as first biopsy increased from 24% in 1996 to 76% in 2005. Accordingly, the number of biopsies needed to achieve a final diagnosis increased over time: In 1996, 91% of final pathology results were achieved with first biopsy, whereas in 2005, only 77% of the cases were finalized after one biopsy.

Pure ADH. Of the 30,953 exams with biopsies, 1,064 (3.4%) women had a final result of pure ADH. Diagnosis of pure ADH was higher among women with a family history of breast cancer, perimenopausal women, and current postmenopausal HT users (Table 2). After adjusting for mammography registry and other patient factors, the rate of pure ADH was significantly higher among women with a family history of breast cancer [odds ratios (OR), 1.25; 95% confidence interval (95% CI), 1.04-1.50], perimenopausal women (OR, 1.75 compared with postmenopausal women; 95% CI, 1.07-2.73), and current postmenopausal HT users (OR, 1.54; 95% CI, 1.29-1.83); the rate of pure ADH changed significantly over time ($P < 0.0001$; Table 3). Rates of ADH (per 10,000 mammograms) decreased over time, after peaking in 1999, with a second drop starting in 2002 (5.5/10,000 mammograms in 1999 to 4.4/10,000 in 2002 to 2.4/10,000 in 2005). This decrease was most apparent in the 50- to 69-year age group, where the rate of ADH decreased from 6.2/10,000 mammograms in 1999 to 4.2/10,000 to 4.4/10,000 in 2000-2002, with a second decrease to 2.1/10,000 in 2005 (Fig. 2A).

Table 2. Unadjusted rates per 10,000 screening mammograms of pure ADH, cancer with ADH, and cancer with no ADH by patient characteristics

	Pure ADH	Cancer with ADH in same breast	Cancer without ADH
Age at mammography, y			
40-49	4.1	2.5	18.9
50-59	4.9	3.2	30.5
60-69	4.5	3.5	40.6
70-79	3.5	5.1	49.0
80+	3.3	4.0	58.1
Family history of breast cancer			
No	4.3	3.3	30.6
Yes	5.7	6.0	48.0
Menopausal status			
Pre	4.4	3.6	22.1
Peri	7.3	4.7	28.6
Post	4.3	3.7	38.8
HT use			
No	3.9	3.5	30.6
Yes	5.4	3.6	36.6
Time since last mammography, y			
<1	6.1	4.5	37.7
1	4.2	3.2	30.7
2	4.1	3.9	38.8
3	5.8	3.6	41.5
4-5	3.7	5.2	47.4

NOTE: Cancer with ADH in the same breast included all cases with pathology results including both cancer and ADH diagnosed within 3 mo of first biopsy, in the same breast.

Table 3. ORs and 95% CIs from logistic regression models fit separately for each outcome and adjusting for variables in table as well as mammography registry, time since last mammogram, and year of screening mammogram

	Pure ADH	Cancer with ADH in same breast*	Cancer without ADH
Age at mammography, y			
40-49	0.82 (0.65-1.03)	**0.65 (0.49-0.86)**	0.57 (0.51-0.63)
50-59	Reference group	Reference group	Reference group
60-69	1.06 (0.87-1.28)	**1.25 (1.00-1.55)**	1.39 (1.29-1.49)
70-79	0.87 (0.68-1.10)	**1.84 (1.47-2.31)**	1.70 (1.57-1.83)
80+	0.83 (0.54-1.22)	1.20 (0.80-1.74)	1.85 (1.66-2.06)
Family history of breast cancer			
Yes vs no	**1.25 (1.04-1.50)**	**1.63 (1.36-1.95)**	**1.46 (1.37-1.55)**
Menopausal status			
Post	Reference group	Reference group	Reference group
Pre vs post	1.28 (.98-1.70)	**1.52 (1.12-2.08)**	**1.25 (1.11-1.39)**
Peri vs post	**1.75 (1.07-2.73)**	1.34 (0.74-2.23)	1.04 (0.82-1.29)
HT use			
No	Reference Group	Reference Group	Reference Group
Yes	**1.54 (1.29-1.83)**	**1.38 (1.14-1.67)**	**1.27 (1.19-1.35)**
Time since last mammography, y			
<1	1.12 (0.67-1.73)	**1.78 (1.07-2.76)**	1.47 (1.24-1.74)
1	Reference group	Reference group	Reference group
2	1.04 (0.85-1.27)	**1.30 (1.06-1.60)**	**1.25 (1.16-1.33)**
3	**1.53 (1.12-2.04)**	**1.51 (1.04-2.11)**	**1.54 (1.37-1.72)**
4-5	0.77 (0.41-1.31)	**2.22 (1.43-3.27)**	**1.95 (1.68-2.24)**
Exam year			
1996	**0.55 (0.35-0.83)**	**0.38 (0.19-0.69)**	**0.73 (0.63-0.85)**
1997	0.91 (0.68-1.21)	0.76 (0.51-1.11)	**0.80 (0.71-0.91)**
1998	1.04 (0.80-1.35)	0.94 (0.67-1.33)	1.04 (0.93-1.16)
1999	Reference group	Reference group	Reference group
2000	**0.63 (0.47-0.83)**	1.07 (0.78-1.48)	0.91 (0.82-1.01)
2001	**0.74 (0.56-0.97)**	1.10 (0.80-1.52)	0.96 (0.87-1.07)
2002	0.82 (0.63-1.06)	**1.37 (1.01-1.86)**	0.97 (0.88-1.08)
2003	0.78 (0.58-1.04)	**1.45 (1.07-1.98)**	1.03 (0.92-1.14)
2004	**0.67 (0.49-0.91)**	0.96 (0.68-1.35)	0.98 (0.88-1.09)
2005	**0.58 (0.42-0.81)**	1.13 (0.82-1.58)	1.00 (0.89-1.11)

NOTE: ORs in boldface are statistically significant at the 0.05 level.
*Cancer with ADH in the same breast included all cases with pathology results including both cancer and ADH diagnosed within 3 mo of first biopsy, in the same breast.

ADH Associated with Cancer. We found 833 cases of cancer with ADH in the same breast (versus 8,161 of cancer without ADH). Rates of upgrade in diagnosis from ADH to cancer with excisional biopsy increased from 4% in the 1990s to approximately 10% in the last 4 years of the study. After adjustment for mammography registry and other patient factors, rates of cancer with ADH were highest in the 70- to 79-year age group (OR, 1.84 compared with 50-59; 95% CI, 1.47-2.31), in women with a family history of breast cancer (OR, 1.63; 95% CI, 1.36-1.95), and in current postmenopausal HT users (OR, 1.38; 95% CI, 1.14-1.67; Table 3). The rates of cancer (both invasive and DCIS) with ADH increased from 1.5/10,000 mammograms in 1996 to a peak of 4.3/10,000 mammograms in 2002 and then decreased slightly to 3.3/10,000 mammograms in 2005 (Fig. 2B). This contrasts with the rates of cancer without ADH, which decreased from 36/10,000 mammograms in 1998 to 27/10,000 in 2005 (Fig. 2C), a trend that disappeared after controlling for current use of postmenopausal HT.

All three outcomes seem to have two separate peaks, one around 1998-1999 and the other around 2002, depending on the age group examined.

When compared with cancers without ADH, cancers associated with ADH were more likely to be DCIS (OR, 3.05; 95% CI, 2.61-3.55) and, among invasive cancers, stage I (OR, 1.74; 95% CI, 1.38-2.19; Table 4). Cancer with ADH was more likely to be low grade (grade 1 or 2) when compared with cancer with no ADH (OR for DCIS, 2.38; 95% CI, 1.73-3.28; OR for invasive cancers, 1.70; 95% CI, 1.33-2.19; Table 4). Ninety percent of invasive cancers with ADH were estrogen receptor positive, compared with 83% of cancers without ADH (OR, 1.77; 95% CI, 1.26-2.57). Similarly invasive cancers with ADH were more likely to be progesterone receptor positive (OR, 1.43; 95% CI, 1.10-1.89).

Discussion

We examined patient characteristics and rates of ADH with and without cancer in a population of women screened with mammography. Because the diagnosis of ADH is associated with the use of mammography, we chose to examine a screened population to minimize the trends that are due to changes in use of screening mammography over time. We found that the rates of both ADH and cancer associated with ADH were significantly increased among women with a positive family history of breast cancer and current postmenopausal HT users.

When examining risk factors for ADH, several reports found a positive association between increasing age and rates of ADH (1, 6, 14, 15), whereas others did not (2). None of these studies adjusted rates for other possible risk factors associated with ADH and age. In our population, the highest rates of ADH were in the 50- to 59-year age group; however, after adjusting these rates for risk factors, ADH was not significantly associated with age.

Similar to our finding of a significant association between use of postmenopausal HT and ADH, women in the Nurses' Health Study with ADH were more likely to have used postmenopausal HT for more than 5 years than were women with proliferative biopsies without atypia or nonproliferative breast biopsies (6). The Women's Health Initiative found a higher rate of benign proliferative breast disease in women using estrogen plus progestin (16). A higher rate of atypical hyperplasia was not found in these women, but the authors noted the small numbers of biopsies with atypical hyperplasia in their study. Earlier studies found no association between use of postmenopausal HT and ADH (17). It is difficult to compare the different study results because postmenopausal HT composition has changed over time (i.e., combined estrogen and progesterone versus estrogen alone) and the exact treatment is not available in most studies, including ours.

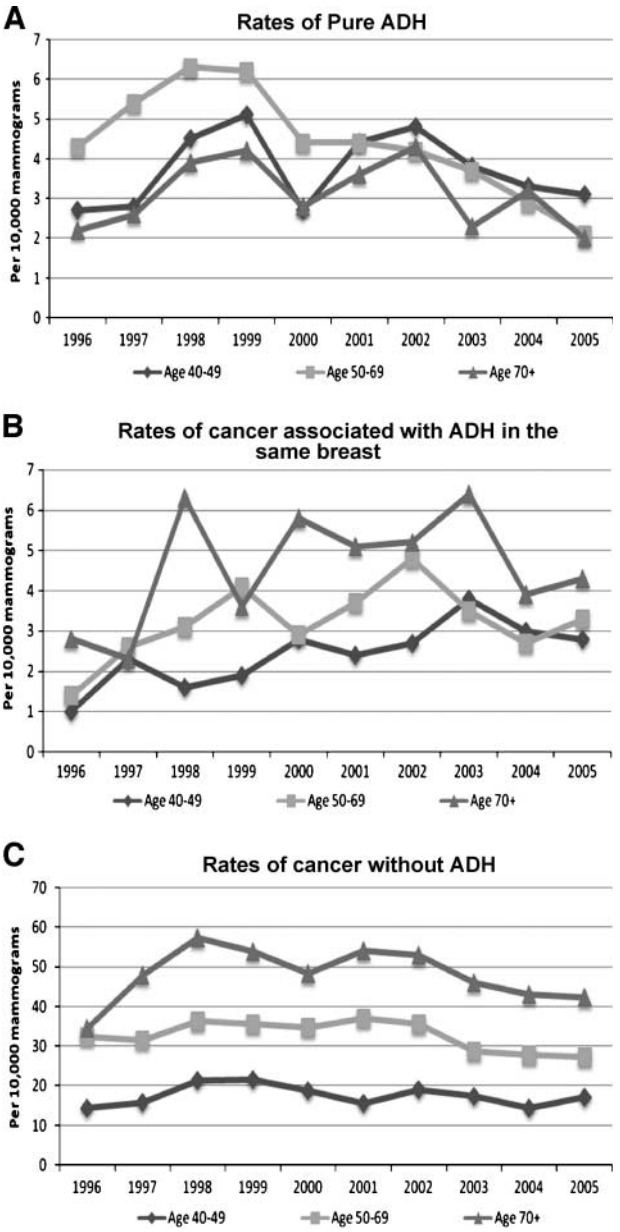

Figure 2. Rates per 10,000 screening mammograms, by age group, adjusted for age, time since last mammogram, and registry. **A.** rates of pure ADH. **B.** rates of cancer associated with ADH in same breast. **C.** rates of cancer without ADH.

As for family history, Webb et al. (14) reported an association between atypical hyperplasia and a positive family history (when comparing to women with benign breast biopsy with no atypia) in the Nurses' Health Study II participants, and Hartmann found a similar association using the Mayo Clinic data set (15), consistent with our results. Others have not found such an association (2).

In our study, we found ADH in 3.4% of biopsies done within 1 year of screening mammography in women with a screening examination within the previous 5 years. Reported rates of ADH vary widely from 2% to 12% of biopsies across studies (1, 18, 19). Page et al. (1) reported a rate of 2% in all surgical biopsies done between 1950 and 1968, whereas de Mascarel et al. (18) included all surgical biopsies for microcalcifications between 1975 and 2002 and found a rate of 8%. Eby et al. (19) reported even higher rates in percutaneous biopsies in Seattle, Washington (12% after excluding cases upgraded to cancer), which they hypothesized was due to geographic variance. Other explanations of the variability in rates include the specimen analysis protocol; de Mascarel et al. (18) report the most exhaustive analysis (median of 26 slides per specimen, compared with 1-5 slides in most of the cases Page reported), hence the higher rate of abnormal findings in this study. Page et al. (1) previously noted this finding: As the number of slides per specimen examined increases, a higher rate of atypical lesions is identified. Another reason for variation may be different definitions of ADH, some including other lesions such as flat epithelial atypia and atypical columnar hyperplasia.

Reported rates of ADH associated with cancer also vary considerably. In this study, 7% of invasive cancers were associated with ADH in the same breast, as were 19% of DCIS cases. Fowble et al. (20) found ADH in 22% of patients undergoing breast-conserving surgery for invasive carcinoma. This rate, however, was significantly increased from a previous report from the same center, which emphasizes the fact that rates of ADH are associated not only with the study population and criteria for diagnosis but also with the effort made to identify it.

The recent decrease in incidence of breast cancer in the United States has been ascribed to the decreased use of postmenopausal HT (10-12, 21-24), suggesting a role for postmenopausal HT as a promoter of breast cancer. Use of postmenopausal HT in our population decreased since 2000 in the 40- to 49-year age group and since 2001 in the 50- to 69-year and 70+-year age groups. The rates of pure ADH in the same population decreased in 1999-2000 and again starting in 2002. Changes in use of postmenopausal HT may explain the second decline that occurred in the rates of ADH. The rates of cancer associated with ADH decreased after peaking in 2002-2003, depending on the age group. Use of postmenopausal HT has been associated with higher rates of both advanced and early-stage breast cancers (25, 26), as well as higher rates of breast biopsies in general (25) and benign proliferative breast disease (16, 27). Postmenopausal HT may promote breast epithelium proliferation differently depending on genetic mutations and patient risk factors, resulting in increased rates of ADH, early cancer, and advanced cancer.

Table 4. Tumor characteristics of cancers associated with ADH in same breast and cancers without ADH

	Cancer with ADH in same breast,* *n* (%)	Cancer with no ADH, *n* (%)	ORs and 95% CI
Total	833	8,161	
DCIS	357 (45)	1,512 (20)	**3.05 (2.61-3.55)**
Invasive carcinoma	476 (57)	6,649 (81)	
DCIS cancer grade (27% missing)			
1	55 (22)	166 (15)	**2.38 (1.73-3.28)**†
2	109 (43)	361 (33)	
3 or 4	90 (35)	578 (52)	
Invasive cancer characteristics			
Histology (7% missing)			
Ductal	345 (79)	5,033 (82)	0.87 (0.59-1.24)‡
Lobular	35 (8)	529 (9)	
Mixed ductal and lobular	53 (12)	553 (9)	
Other	3 (1)	42 (1)	
Grade (15% missing)			
1	131 (33)	1,406 (25)	**1.70 (1.33-2.19)**†
2	176 (44)	2,452 (43)	
3 or 4	89 (22)	1,837 (32)	
AJCC stage 5th edition (8% missing)			
I	322 (74)	3,841 (63)	**1.74 (1.38-2.19)**§
II	97 (22)	1,896 (31)	
III or IV	14 (3)	398 (6)	
Estrogen receptor status (18% missing)			
Positive	341 (90)	4,519 (83)	**1.77 (1.26-2.57)**
Negative	37 (10)	924 (17)	
Progesterone receptor status (20% missing)			
Positive	300 (80)	3,851 (73)	**1.43 (1.10-1.89)**
Negative	71 (19)	1,430 (27)	

NOTE: ORs and 95% CIs from logistic regression models fit separately for each cancer characteristic and were adjusted for mammography registry, time since last mammogram, and year of screening mammogram. ORs in boldface are statistically significant at the 0.05 level. Percentages exclude missing values.
Abbreviation: AJCC, American Joint Committee on Cancer.
*Cancer with ADH in the same breast included all cases with pathology results including both cancer and ADH diagnosed within 3 mo of first biopsy, in the same breast.
†Low grade (1 + 2) vs high grade.
‡Ductal vs other.
§Stage I vs others.

The trend in rates of cancer associated with ADH (peaking in 2002-2003, then decreasing) may be explained by differences in pathologic reporting of the benign tissue surrounding cancer and the increased use of core biopsies. It is possible that when excisional biopsies were used as the first biopsy, the entire lesion was excised and the pathologist limited the report to the most severe diagnosis in the specimen, reducing the reporting of ADH associated with cancer. Although we found an association between cancer with ADH and use of core biopsy as first biopsy, controlling for type of first biopsy did not change the trends in rates of cancer associated with ADH over time (data not shown). Changes in the definition of ADH may have contributed to these changes as well because the diagnosis of ADH and that of low-grade DCIS can overlap; however, overall rates of DCIS with ADH were stable since 1998 (data not shown). The decrease in cancer with ADH since 2002-2003 may be due to other variables that this study did not examine, such as increased use of tamoxifen. However, the decrease cannot be explained by decreases in screening utilization because we examined women undergoing screening mammography and controlled for the time since last screening mammography.

In our patient population, cancer associated with ADH was more likely to be of low stage and low grade and estrogen and progesterone receptor positive when compared with cancer with no associated ADH. An association with low stage (18, 20) and low grade (18) was previously reported. These findings support the theory of separate pathways for low-grade and high-grade breast cancers, with ADH possibly being a precursor of some low-grade cancers. We found a nonsignificant increase with mixed ductal and lobular cancers; others reported an association with invasive lobular and tubular carcinoma (18).

This is the largest study reviewing patients with ADH. However, our study has several limitations. First, no central pathologic review of the slides was done, and the diagnosis of ADH is complicated and may differ by mammography registry and over time. Therefore, all three groups of outcomes may include patients with incorrect diagnoses either because of under- or over-diagnosis. This misclassification can cause underestimation or overestimation of the associations we found. The diagnosis of cancer with ADH was based on the finding of both diagnoses in the same patient in the same breast within 3 months from the first biopsy. Therefore, patients diagnosed with cancer and ADH in the same breast may actually have these two diagnoses in two separate foci. The cohort of patients is not constant over time, as can be seen from the fairly constant age of the cohort over the 10 years; therefore, a certain percentage of women are lost every year, and new women are continually added. In an attempt to examine the trend in diagnosis of ADH in a screened population, we included only women with a prior screening mammogram within 5 years. This selection criterion, on the one hand, may limit the generalizability of our results because women undergoing regular mammography screening have been shown to be a selected group of women. On the other hand, more than 70% of women undergo screening mammography so that our results apply to a large proportion of women.

Finally, association between use of postmenopausal HT and different outcomes is limited to current use of any postmenopausal HT at the time of the mammogram. Our findings relate only to current users of postmenopausal HT. As the data set does not include the type of HT, the associations found are probably due to the use of combined estrogen and progesterone treatment because only combined therapy has been shown to increase the risk breast cancer.

In conclusion, ADH with and without cancer is associated with use of postmenopausal HT. Rates of ADH and cancer associated with ADH in this screened population have decreased over time. This finding may be partially explained by the decrease in rates of use of postmenopausal HT.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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References

1. Page DL, Dupont WD, Rogers LW, Rados MS. Atypical hyperplastic lesions of the female breast. A long-term follow-up study. Cancer 1985;55:2698–708.
2. Stomper PC, Cholewinski SP, Penetrante RB, Harlos JP, Tsangaris TN. Atypical hyperplasia: frequency and mammographic and pathologic relationships in excisional biopsies guided with mammography and clinical examination. Radiology 1993;189:667–71.
3. Dupont WD, Page DL. Risk factors for breast cancer in women with proliferative breast disease. N Engl J Med 1985;312:146–51.
4. Page DL, Dupont WD. Anatomic markers of human premalignancy and risk of breast cancer. Cancer 1990;66:1326–35.
5. Page DL. Breast lesions, pathology and cancer risk. Breast J 2004;10:S3–4.
6. Collins LC, Baer HJ, Tamimi RM, Connolly JL, Colditz GA, Schnitt SJ. Magnitude and laterality of breast cancer risk according to histologic type of atypical hyperplasia. Results from the Nurses' Health Study. Cancer 2007;109:180–7.
7. Simpson PT, Reis-Filho JS, Gale T, Lakhani SR. Molecular evolution of breast cancer. J Pathol 2005;205:248–54.
8. Viacava P, Naccarato AG, Bevilacqua G. Different proliferative patterns characterize different preinvasive breast lesions. J Pathol 1999;288:245–51.
9. Abdel-Fatah TM, Powe DG, Hodi Z, et al. High frequency of coexistence of columnar cell lesions, lobular neoplasia, and low grade ductal carcinoma *in situ* with invasive tubular carcinoma and invasive lobular carcinoma. Am J Surg Pathol 2007;31:417–26.
10. Clarke CA, Glaser SL, Uratsu CS, Selby JV, Kushi LH, Herrinton L. Recent declines in hormone therapy utilization and breast cancer incidence: clinical and population-based evidence. J Clin Oncol 2006;24:e49–50.
11. Ravdin PM, Cronin KA, Howlader N, et al. The decrease in breast-cancer incidence in 2003 in the United States. N Engl J Med 2007;356:1670–4.
12. Jemal A, Ward E, Thun MJ. Recent trends in breast cancer incidence rates by age and tumor characteristics among U.S. women. Breast Cancer Res 2007;9:R28.
13. Fleming ID, Cooper JS, Henson DE, et al, editors. AJCC cancer staging manual. 5th ed Philadelphia (PA): Lippincott-Raven; 1997.
14. Webb PM, Byrne C, Schnitt SJ, et al. Family history of breast cancer, age and benign breast disease. Int J Cancer 2002;100:375–8.
15. Hartmann LC, Sellers TA, Frost MH, et al. Benign breast disease and the risk of breast cancer. N Engl J Med 2005;353:229–37.
16. Rohan TE, Negassa A, Rowan T, et al. Estrogen plus progestin and risk of benign proliferative breast disease. Cancer Epidemiol Biomarkers Prev 2008;17:2337–43.
17. Friedenreich CM, Bryant HE, Alexander F, Hugh J, Danyluk J, Page DL. Risk factors for benign proliferative breast disease. Int J Epidemiol 2000;29:637–44.
18. de Mascarel I, MacGrogan G, Mathoulin-Pelissier S, et al. Epithelial atypia in biopsies performed for microcalcifications. Practical considerations about 2,833 serially sectioned surgical biopsies with a long follow-up. Virchows Arch 2007;451:1–10.
19. Eby PR, Ochsner JE, DeMartini WB, Allison KH, Peacock S, Lehman CD. Frequency and upgrade rates of atypical ductal hyperplasia diagnosed at stereotactic vacuum-assisted breast biopsy: 9-versus 11-gauge. AJR Am J Roentgenol 2009;192:229–34.
20. Fowble B, Hanlon AL, Patchefsky A, et al. The presence of proliferative breast disease with atypia does not significantly influence outcome in early-stage invasive breast cancer treated with conservative surgery and radiation. Int J Radiat Oncol Biol Phys 1998;42:105–15.
21. Colditz GA. Decline in breast cancer incidence due to removal of promoter: combination estrogen plus progestin. Breast Cancer Res 2007;9:108.
22. Katalinic A, Rawal R. Decline in breast cancer incidence after decrease in utilisation of hormone replacement therapy. Breast Cancer Res Treat 2008;107:427–30.
23. Glass AG, Lacey JV, Jr., Carreon JD, Hoover RN. Breast cancer incidence, 1986-2006: combined roles of menopausal hormone therapy, screening mammography and estrogen receptor status. J Natl Cancer Inst 2007;99:1152–61.
24. Kerlikowske K, Miglioretti DL, Buist DSM, Walker R, Carney PA. Declines in invasive breast cancer and use of postmenopausal hormone therapy in a screening mammography population. J Natl Cancer Inst 2007;99:1335–9.
25. Chlebowski RT, Hendrix SL, Langer RD, et al. Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women. The Women's Health Initiative randomized trial. JAMA 2003;289:3243–53.
26. Kerlikowske K, Miglioretti DL, Ballard-Barbash R, et al. Prognostic characteristics of breast cancer among postmenopausal hormone users in a screened population. J Clin Oncol 2003;21:4314–21.
27. Rohan TE, Negassa A, Chlebowski RT, et al. Conjugated equine estrogen and risk of benign proliferative breast disease: a randomized controlled trial. J Natl Cancer Inst 2008;100:563–71.

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