HORM CANC (2010) 1:93–99
DOI 10.1007/s12672-010-0011-0

The Relationship Between Hormone Therapy Use at the Time of Diagnosis of Breast Cancer and Tumor Characteristics

Mary Panjari · Robin Bell · Marijana Lijovic · Maria La China · Max Schwarz · Pamela Fradkin · Jo Bradbury · Helen Farrugia · Susan R. Davis

Received: 8 November 2009 / Accepted: 31 January 2010 / Published online: 9 March 2010

Abstract Exposure to postmenopausal hormone therapy (HT) may affect the stage, histological type, and hormone receptor (HR) status of invasive breast cancer at the time of diagnosis. One thousand six hundred eighty-four women with newly diagnosed first invasive breast cancer were recruited to the "MBF Foundation Health and Wellbeing after Breast Cancer Study." Women using systemic HT estrogen (E) or E combined with progesterone (P) at the time of diagnosis of breast cancer were compared with those not using HT. Breast cancer tumor data were obtained from the Victorian Cancer Registry. Regression analysis was used to determine the associations between HT use or not at the time of diagnosis and tumor histology (ductal vs lobular), stage (I vs II, III, IV), HR status (ER+ or PR+ or both vs ER− or PR−). Of 1,377 women included in the analysis, 226 (16%) were using HT at the time of diagnosis. Of HT users, 20.4% had lobular breast cancer, 50% were stage I, and 85.8% had HR-positive tumors. Of non-users, 13.6% had lobular breast cancer, 48.2% were stage I, and 82.4% had HR-positive tumors. Use of systemic HT was associated with increased odds of having lobular compared with ductal breast cancer (OR=1.75, 95% CI= 1.14–2.69, p=0.01). There were no associations between HT use and either breast cancer stage or HR status. Women using systemic HT at the time of diagnosis were more likely to have lobular rather than ductal breast cancer compared with women not on HT.

Keywords Women's health · Hormones · Breast cancer · Histology

M. Panjari (✉) · R. Bell · M. Lijovic · M. La China · P. Fradkin · J. Bradbury · S. R. Davis
Women's Health Program, Department of Medicine,
Monash University Medical School, Alfred Hospital,
Commercial Road,
Prahran, VIC, Australia 3181
e-mail: mary.panjari@med.monash.edu.au

M. Schwarz
Department of Medicine, Monash University Medical School,
Alfred Hospital,
Commercial Road,
Prahran, VIC, Australia 3181

M. Schwarz
Alfred Hospital, Bayside Health,
Commercial Road,
Prahran, VIC, Australia 3181

H. Farrugia
Victorian Cancer Registry, The Cancer Council Victoria,
Carlton, VIC 3053, Australia

Introduction

Whether the use of postmenopausal hormone therapy (HT) influences the stage and histological characteristics of invasive breast cancer at diagnosis remains controversial. Whereas some studies suggest that HT use is associated with diagnosis at an earlier stage [1] and hence potentially a better prognosis [2, 3], the Women's Health Initiative (WHI) randomized controlled trial has linked HT use with not only an increase in breast cancer risk but also diagnosis at a later stage [4]. Findings from observational studies may have been confounded by greater surveillance among HT users than non-users and potentially differential access to mammographic screening. The MBF Foundation Health and Wellbeing after Breast Cancer Study (MBF Study) is a prospective, longitudinal study being conducted in the Australian state of Victoria. Women in the study were

recruited within the first year of their diagnosis, primarily through the Victorian Cancer Registry (VCR), and are being followed up annually for 5 years. In Australia, free mammographic screening is available every 2 years for women aged over 40 with a two-yearly recall for women in the target age range of 50 to 69 years. The participation rate of women in the target age range in mammographic screening in Victoria is about 60% [5] and, as we have previously reported, the women in our cohort are representative of all women newly diagnosed in Victoria with invasive breast cancer in terms of age, size of tumor at diagnosis, and location of residence [6]. Thus, this cohort provides the opportunity to examine whether postmenopausal HT use at diagnosis is associated with tumor stage, specific histology, and hormone receptor (HR) status in a large prospective community-based study in an environment where mammographic screening is available at no cost.

Methods

Study Population

Study eligibility, recruitment process, and enrolment have been described in full elsewhere [6]. In brief, 1,684 Victorian women newly diagnosed with their first invasive breast cancer were recruited to the MBF Study during the period from June 2004 to December 2006, either via a public awareness campaign or by direct written invitation from the VCR. Approximately 80% of the sample was recruited directly through the VCR. Two thousand one hundred thirty-five women agreed to participate; of these, 1,747 returned a questionnaire; however, 63 were ineligible due to not meeting the study criteria. Of the women who were directly invited by the VCR, 16% refused participation. The definitive diagnostic information was obtained by individual data linkage with the VCR from the pathology report which may have been of a surgical specimen or a core biopsy.

Women were eligible to participate in the MBF Study if the date of their first diagnosis of invasive breast cancer was after 1 June 2004 and within 12 months of study enrolment, they were 18 years of age or older, resided in Victoria, had histological confirmation of primary invasive breast cancer excluding ductal carcinoma in situ, Phyllodes tumor, Paget's disease, lymphoma and sarcoma, and had good comprehension of English.

For the purpose of this analysis, women who reported using tibolone, vaginal estrogen (E), androgens, compounded hormonal preparations, natural therapies, dehydroepiandrosterone, or progesterone were excluded, unless they were also using systemic E. Women using hormonal contraception and women younger than age 40 years were also excluded, as HT users <40 years would be considered to have premature menopause and women the same age not on HT would all be premenopausal. Women classified as systemic HT users reported using E alone or in combination with progesterone (P).

The study was approved by the Human Research Ethics Committee of The Cancer Council Victoria, the Standing Committee on Ethics in Research Involving Humans, Monash University and recruitment was supported by more than 50 Victorian hospitals and health centers. All participants gave written informed consent.

Data Collection

Participants completed an enrolment questionnaire at the time of recruitment on average 40 weeks from the time of diagnosis. The enrolment questionnaire included questions about the breast cancer, breast cancer treatment, demographics, and hormone (contraception and HT) use.

HT use was assessed by the question “have you ever taken hormone therapy?” (yes or no) and “were you taking hormone therapy when your breast cancer was diagnosed?” (yes or no). Further questions covered years of use and number of years since stopping (<2, 2–5, 6–10, and >10 years). The type of HT taken at the time of diagnosis was identified by participants from a list of all available options by name and included combined EP tablets or patches, E only tablets, E implant, E gel, E nasal spray, vaginal E, P only tablets or creams, androgen therapy, and tibolone.

Breast Cancer Characteristics

Tumor, nodes, and metastasis data for each woman's breast cancer were provided by the VCR. Cancer staging was according to the sixth edition of the Cancer Staging Manual [7]. For this study, women were classified into two groups as stage I or beyond stage I (II, III, and IV) at diagnosis (stage I disease refers to breast cancer tumor ≤20 mm in size with no evidence of breast cancer cells in the lymph nodes or other parts of the body; breast cancer beyond stage I are >20 mm or breast cancer cells have been found in the lymph nodes and/or other parts of the body).

Histological information was obtained from the VCR and breast cancer was classified as ductal (ICD-02 International Classification of Diseases histology codes 8500, 8022, 8035, 8211, 8201, 8503, 8401, 8575, 8314, and 8502) or lobular (code 8520). Mixed ductal/lobular breast cancer (code 8522) was included with lobular. Any other breast cancer codes in this cohort were excluded from the analyses (n=69, 5%).

HR status (positive or negative) data were obtained from the VCR. Women were classified as positive if they were estrogen receptor (ER) positive, progesterone receptor (PR) positive, or both.

Statistical Analysis

Women using systemic HT at the time of diagnosis of breast cancer were compared to women not using HT. The relationships between histology, cancer stage, receptor status, and systemic HT (E only or combined EP) use at the time of diagnosis of breast cancer were investigated by multivariate logistic regression which was adjusted for age. Age categories 40–49, 50–59, 60–69, and 70+ were entered into the equation as three separate variables, with 70+ as the reference category. The analyses were first performed separately for E alone and E + P and then the two groups were combined. The analyses were also performed with adjustment for body mass index (BMI) and education level. Finally, the analyses were performed with only never users in the non-user group. Statistical analyses were performed using SPSS 17.0 for Windows (SPSS Inc. Chicago, IL, USA).

Results

One thousand six hundred eighty-four study participants were recruited to the study. One woman was subsequently excluded due to a prior diagnosis of invasive breast cancer. Of the remaining 1,683 participants, 1,377 women were included in the analyses. Three hundred seven women were excluded as follows: tibolone n=22, (vaginal estrogen only, androgens, DHEA, compounded hormones, natural therapy) n=105, hormonal contraception n=116, progesterone only n=3, age <40 years n=60, not primary BC diagnosis n=1. Of these 1,377 women, 226 were using systemic E or EP and 1,151 women were not on HT. Seventy-two women were using E only therapy and 154 were using combined EP. Of the 1,151 women not using HT at diagnosis of breast cancer, 28% had ceased HT before diagnosis and 72% were never users. Of the past users who had ceased, only 20% had stopped within the 2 years before diagnosis. Of past users, 63% had used HT for <5 years and 37% for five or more years. This is in contrast to the current HT users as 71.4% had used HT for ≥5 years.

The characteristics of the 1,377 women included in the analyses are presented in Table 1. At diagnosis, HT users were slightly older (mean age ± SD=61.09±7.53 years) than women not using HT at diagnosis (59.52±11.41 years; mean difference=−1.57, 95% CI=−2.75, −0.38, p=0.01). Mean tumor size was 17.26±12.24 mm in HT users and 19.08±12.24 mm in non-users; however, the difference was not statistically significant (rank test z=−1.4, p=0.2).

As there were no differences between E only and EP users (Tables 2 and 3) for any of the outcomes of interest, these two groups were combined and the analysis repeated as systemic HT use at the time of diagnosis vs no HT (Table 4). HT use at diagnosis was associated with increased odds of lobular rather than ductal breast cancer (1.55, 95% CI=1.06, 2.25, p=0.02; Table 4). There were no associations between cancer stage (stage I vs greater than stage I) and use of systemic HT compared with non-use (Table 4). There were no associations between HR status (negative vs positive) and use of systemic HT (Table 4). All of these odds ratios were age-adjusted, treating age categorically by decade. If age was treated as a continuous variable, the findings were unchanged. The analyses were also adjusted for BMI (treated as a continuous variable) and education; however, the results did not change (data not shown). Consistent with the fact that most non-users of HT at diagnosis were never users of HT, when the analyses were repeated with only never users in the non-user group, the findings were unchanged (data not shown). Also consistent with the observation that 71.4% of current users had used HT for ≥5 years, when "current users" were restricted to those women who had used for ≥5 years only, the findings were also unchanged. The analyses were also repeated excluding the women with mixed ductal/lobular breast cancer. The results did not change (data not shown).

Discussion

In this cohort of women with invasive breast cancer, use of systemic HT at diagnosis was associated with increased likelihood of having lobular compared with ductal carcinoma. No associations between breast cancer stage or HR status and use of HT at diagnosis were observed.

Our results are consistent with the association between HT use and invasive lobular breast cancer seen in the Million Women Study [8] and several other observational studies [9–14]. Furthermore, it has been reported in the USA that, as the number of HT users increased from the 1970s onwards, there was a steady increase in lobular but not ductal breast cancer incidence in women older than 50 years of age [15, 16]. It is not yet clear if this trend is reversed with the decrease in HT use since the publication of the results of the WHI trials.

The association between HT use and lobular breast cancer might be clinically important. Although invasive lobular breast cancer is less common than ductal, accounting for only 8–14% of all breast cancers [17, 18], it can be more difficult to diagnose. The histology of lobular breast cancer is different from ductal and characterized by small, round cells that are bland in appearance and have a diffusive pattern of infiltration that does not destroy anatomic structures or provoke substantial connective tissue response. They often fail to form distinct masses due to lack of desmoplastic reaction which makes the lesions less easily detected by palpation or mammography [19, 20]. Up to 19% false-negative mammographic diagnoses have been reported

Table 1 Characteristics of cohort (n=1,377)

Characteristic	HT at diagnosis (n=226)[a] Frequency (%)	No HT at diagnosis (n=1,151) Frequency (%)	Statistic
Age (years)			χ^2=60, df=3, p<0.0001
40–49	9 (4.0)	273 (23.7)	
50–59	103 (45.6)	360 (31.3)	
60–69	81 (35.8)	282 (24.5)	
70+	33 (14.6)	236 (20.5)	
Relationship status			χ^2=0.040, df=2, p=0.98
No partner	32(14.2)	165 (14.3)	
Partner	172(76.1)	878 (76.3)	
Widowed	22 (9.7)	107 (9.3)	
Education			χ^2=1.57, df=1, p=0.21
Lower	72 (37.3)	435 (42.15)	
Higher	121 (62.7)	597 (57.8)	
BMI			χ^2=16.75, df=2, p<0.0001
<18.5	6 (2.7)	14 (1.2)	
18.5–24.9	114 (50.4)	432 (37.5)	
≥25	106 (46.9)	699 (60.7)	
Missing	0	6 (0.5)	
Stage of breast cancer			χ^2=0.24, df=1, p=0.62
Stage I	113 (50.0)	555 (48.2)	
Stage IIA, IIB, IIIA, IIIB, IIIC, IV	113 (50.0)	596 (51.8)	
Histology[b]			χ^2=6.21, df=1, p=0.013
Ductal	172 (78.9)	933 (85.6)	
Lobular	46 (21.1)	157 (14.4)	
HR status[b]			χ^2=2.28 df=1 p=0.13
Estrogen and/or progesterone positive	194 (88.2)	948 (84.2)	
Estrogen and progesterone negative	26 (11.8)	178 (15.8)	
Tumor size (mm), mean ± SD	17.26±12.24	19.08±12.24	Mann–Whitney rank test z=−1.4, p=0.2

HT hormone therapy

[a] Estrogen only, n=72; combined estrogen and progesterone, n=154

[b] Numbers do not add due to small amount of missing data for histology and HR status

Systemic HT includes combined estrogen and progesterone tablet, estrogen only tablet, estrogen/progesterone patch, estrogen implant, estrogen gel, estrogen nasal spray, progesterone tablet, progesterone cream

Table 2 Odds ratios for histology, stage, and receptor status E only vs no HT at the time of diagnosis

	Multivariate OR (95% CI); age-adjusted p value
Histology: ductal vs lobular	1.75 (0.97, 3.16); 0.06
Stage: stage I vs stage II, III, IV	1.25 (0.77, 2.02); 0.37
Receptor status: EP− vs EP+	1.24 (0.60, 2.55); 0.56

E only: 53 (76.8) ductal, 16 (23.3) lobular; no HT: 933 (85.6) ductal, 157 (14.4) lobular

E only: 32 (44.9) stage I, 40 (55.6) stage II, III, IV; no HT: 555 (48.2) stage I 596 (51.8), stage II, III, IV

E only: 9 (12.7) EP−, 62 (87.3) EP+; no HT: 178 (15.8) EP−, 948 (84.5) EP+

n(%)

Table 3 Odds ratios for histology, stage, and receptor status and E + P vs no HT at the time of diagnosis

	Multivariate OR (95% CI); age-adjusted p value
Histology: ductal vs lobular	1.46 (0.94, 2.28); 0.09
Stage: stage I vs stage II, III, IV	0.88 (0.63, 1.25); 0.48
Receptor status: EP− vs EP+	1.46 (0.85, 2.50); 0.17

EP: 119 (79.9) ductal, 30 (20.1) lobular; no HT: 933 (85.6) ductal, 157 (14.4) lobular

EP: 81(52.6) stage I, 73 (47.4) stage II, III, IV; no HT: 555 (48.2) stage I, 596 (51.8) stage II, III, IV

EP: 17 (11.4) EP−, 132 (88.6) EP+; no HT: 178 (15.8) EP−, 948 (84.5) EP+

n(%)

Table 4 Odds ratios for histology, stage, and receptor status and systemic HT vs no HT at the time of diagnosis

	Multivariate OR (95% CI); age-adjusted *p* value
Histology: ductal vs lobular	1.55 (1.06, 2.25); 0.02
Stage: stage I vs stage II, III, IV	0.99 (0.74, 1.32); 0.94
Receptor status: EP− vs EP+	1.37 (0.87, 2.14); 0.17

to be due to the uniform, bland appearance of the tumor cells and the subtle changes that may mimic normal breast tissue [21–23]. Ultrasound is more sensitive in detecting lobular breast cancer; however, the false-negative rate is reportedly 12.3% [22, 23]. Furthermore, as HT increases breast density which in turn decreases the sensitivity and specificity of mammography, lobular breast cancer is less easily detected [21, 22, 24]. Due to its cellular nature, lobular breast cancer can be difficult to discern during surgery, making it tricky to achieve tumor-free margins, sometimes resulting in the need for re-excision [19]. As a result, the management of women with lobular breast cancer may differ from that of women with ductal breast cancer as mastectomy is usually favored by surgeons.

There is some evidence from previous studies that lobular breast cancer has a more favorable prognosis than ductal breast cancer [25, 26] although not all agree [20]. Lobular breast cancer is associated with less aggressive tumors with more favorable biologic characteristics [19] and an 11% lower risk of mortality compared with ductal breast cancer [27]. However, since lobular is harder to detect, this may counteract any increase in survival related to the histology alone.

In our study, HT use was not associated with tumor stage. This finding differs from the findings from previous cohort studies which have consistently shown that HT use is associated with earlier stage and smaller size [2, 28–31]. Sener et al., for example, reported that HT use was associated with earlier age at diagnosis, biologically more favorable tumors, and higher survival rates [1]. The findings from the only large randomized placebo-controlled trial, the WHI, were that HT users at diagnosis had larger tumors, had more nodal involvement, and were at a more advanced stage, but there were no significant differences in grade, histology, or receptor status between HT and placebo users [4].

The differences between the findings of the WHI and other observational studies may in part have been due to greater medical surveillance of HT users in observational studies. Women using HT will have regular medical care and may undergo more frequent mammographic screening resulting in earlier diagnosis. We found no difference in tumor stage between HT users and non-users. Australia has a free national breast screening program for women aged 40 years and over which may have minimized screening bias between HT users and non-users in our study. In addition, any excess in early detection of breast cancer due to more frequent screening could be counterbalanced by increased mammographic density in HT users which limits the sensitivity of tumor detection.

We found no significant difference between HT users and non-users in HR status which concurs with the findings of other studies [29, 32] although others have shown an association between HT and positive ER/PR status [33, 34] and that the number of tumors positive for ER/PR increases with HT use [12].

A major strength of our study is that our sample is representative of all newly diagnosed breast cancer cases in Victoria with a similar distribution of age at diagnosis and tumor size [6]. The proportion of tumors that were ductal and lobular in our study is consistent with that reported by the VCR [5]; however, the VCR does not routinely publish tumor stage and receptor status data.

The main limitation of our study is that it was not a randomized controlled trial and eliminating confounding is a challenge. In our study, HT users were self-selected. Although self-selected users of HT might be more likely under greater medical surveillance, our data on stage at diagnosis suggests that any such effect was small.

Conclusions

In conclusion, the results of this study provide further evidence that systemic HT use increases the risk of lobular breast cancer. We found that HT use at diagnosis did not influence other tumor characteristics that affect breast cancer prognosis.

Acknowledgments The authors wish to thank the study participants for their time and efforts. This study was funded by the MBF Foundation, Novartis Australia, L.E.W. Carty Trust, Connie and Craig Kimberley, The National Health and Medical Research Council of Australia (grant nos. 219279 and 490938), The Jack and Robert Smorgon Families Foundation, and Roy Morgan Research.

Competing Interests The authors declare that they have no competing interests.

Authors' Contributions MP conducted statistical analysis and drafted the manuscript. RB conceived of the study, participated in the design, gave statistical analysis advice, and helped draft the manuscript. ML study coordination and participant recruitment. MLC study coordination and participant recruitment. MS participated in the

study design and data interpretation. PF participated in the design and participant recruitment. JB participated in the design and participant recruitment. HF participated in the design, study coordination, and participant recruitment. SD conceived of the study, obtained funding support, participated in the design and conduct, and helped draft the manuscript. All authors have read and approved the final manuscript.

References

1. Sener SF, Winchester DJ, Winchester DP, Du H, Barrera E, Bilimoria M, Krantz S, Rabbitt S (2009) The effects of hormone replacement therapy on postmenopausal breast cancer biology and survival. Am J Surg 197:403–407
2. Christante D, Pommier S, Garreau J, Muller P, LaFleur B, Pommier R (2008) Improved breast cancer survival among hormone replacement therapy users is durable after 5 years of additional follow-up. Am J Surg 196:505–511
3. O'Meara ES, Rossing MA, Daling JR, Elmore JG, Barlow WE, Weiss NS (2001) Hormone replacement therapy after a diagnosis of breast cancer in relation to recurrence and mortality. J Natl Cancer Inst 93:754–762
4. Chlebowski RT, Hendrix SL, Langer RD, Stefanick ML, Gass M, Lane D, Rodabough RJ, Gilligan MA, Cyr MG, Thomson CA, Khandekar J, Petrovitch H, McTiernan A (2003) Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women: the Women's Health Initiative Randomized Trial. JAMA 289:3243–3253
5. Giles GG, Thursfield V (2002) Canstat: breast cancer. The Cancer Council Victoria, Carlton
6. Lijovic M, Davis SR, Fradkin P, La China M, Farrugia H, Wolfe R, Bell RJ (2008) Use of a cancer registry is preferable to a direct-to-community approach for recruitment to a cohort study of wellbeing in women newly diagnosed with invasive breast cancer. BMC Cancer 8:126
7. Sobin L, Wittekind C (eds) (2002) TNM classification of malignant tumors, 6th edn. Wiley-Liss, New York
8. Reeves GK, Beral V, Green J, Gathani T, Bull D, Million Women Study C (2006) Hormonal therapy for menopause and breast-cancer risk by histological type: a cohort study and meta-analysis. Lancet Oncol 7:910–918
9. Li CI, Weiss NS, Stanford JL, Daling JR (2000) Hormone replacement therapy in relation to risk of lobular and ductal breast carcinoma in middle-aged women. Cancer 88:2570–2577
10. Lyytinen H, Pukkala E, Ylikorkala O (2006) Breast cancer risk in postmenopausal women using estrogen-only therapy. Obstet Gynecol 108:1354–1360
11. Newcomer LM, Newcomb PA, Potter JD, Yasui Y, Trentham-Dietz A, Storer BE, Longnecker MP, Baron JA, Daling JR (2003) Postmenopausal hormone therapy and risk of breast cancer by histologic type (United States). Cancer Causes Control 14:225–233
12. Chen C-L, Weiss NS, Newcomb P, Barlow W, White E (2002) Hormone replacement therapy in relation to breast cancer. JAMA 287:734–741
13. Zanetti-Dallenbach RA, Krause EM, Lapaire O, Gueth U, Holzgreve W, Wight E (2008) Impact of hormone replacement therapy on the histologic subtype of breast cancer. Arch Gynecol Obstet 278:443–449
14. Calle EE, Feigelson HS, Hildebrand JS, Teras LR, Thun MJ, Rodriguez C (2009) Postmenopausal hormone use and breast cancer associations differ by hormone regimen and histologic subtype. Cancer 115:936–945
15. Li CI, Anderson BO, Porter P, Holt SK, Daling JR, Moe RE (2000) Changing incidence rate of invasive lobular breast carcinoma among older women. Cancer 88:2561–2569
16. Verkooijen H, Koot V, Fioretta G, van der Heiden M, Schipper M, Rapiti E, Peeters P, Peterse J, Bouchardy C (2008) Hormone replacement therapy, mammography screening and changing age-specific incidence rates of breast cancer: an ecological study comparing two European populations. Breast Cancer Res Treat 107:389–395
17. Borst MJ, Ingold JA (1993) Metastatic patterns of invasive lobular versus invasive ductal carcinoma of the breast. Surgery 114:637–641, discussion 641–632
18. Martinez V, Azzopardi JG (1979) Invasive lobular carcinoma of the breast: incidence and variants. Histopathology 3:467–488
19. Arpino G, Bardou VJ, Clark GM, Elledge RM (2004) Infiltrating lobular carcinoma of the breast: tumor characteristics and clinical outcome. Breast Cancer Res 6:R149–R156
20. Silverstein MJ, Lewinsky BS, Waisman JR, Gierson ED, Colburn WJ, Senofsky GM, Gamagami P (1994) Infiltrating lobular carcinoma. Is it different from infiltrating duct carcinoma? Cancer 73:1673–1677
21. Sala E, Warren R, McCann J, Duffy S, Luben R, Day N (2000) High-risk mammographic parenchymal patterns, hormone replacement therapy and other risk factors: a case–control study. Int J Epidemiol 29:629–636
22. Berg WA, Gutierrez L, NessAiver MS, Carter WB, Bhargavan M, Lewis RS, Ioffe OB (2004) Diagnostic accuracy of mammography, clinical examination, US, and MR imaging in preoperative assessment of breast cancer. Radiology 233:830–849
23. Selinko VL, Middleton LP, Dempsey PJ (2004) Role of sonography in diagnosing and staging invasive lobular carcinoma. J Clin Ultrasound 32:323–332
24. Carney PA, Miglioretti DL, Yankaskas BC, Kerlikowske K, Rosenberg R, Rutter CM, Geller BM, Abraham LA, Taplin SH, Dignan M, Cutter G, Ballard-Barbash R (2003) Individual and combined effects of age, breast density, and hormone replacement therapy use on the accuracy of screening mammography. Ann Intern Med 138:168–175
25. Toikkanen S, Pylkkanen L, Joensuu H (1997) Invasive lobular carcinoma of the breast has better short- and long-term survival than invasive ductal carcinoma. Br J Cancer 76:1234–1240
26. du Toit RS, Locker AP, Ellis IO, Elston CW, Nicholson RI, Robertson JF, Blamey RW (1991) An evaluation of differences in prognosis, recurrence patterns and receptor status between invasive lobular and other invasive carcinomas of the breast. Eur J Surg Oncol 17:251–257
27. Li CI, Moe RE, Daling JR (2003) Risk of mortality by histologic type of breast cancer among women aged 50 to 79 years. Arch Intern Med 163:2149–2153
28. Cheek J, Lacy J, Toth-Fejel S, Morris K, Calhoun K, Pommier RF (2002) The impact of hormone replacement therapy on the detection and stage of breast cancer. Arch Surg 137:1015–1019, discussion 1019–1021
29. Pappo I, Meirshon I, Karni T, Siegelmann-Danielli N, Stahl-Kent V, Sandbank J, Wasserman I, Halevy A (2004) The characteristics of malignant breast tumors in hormone replacement therapy users versus nonusers. Ann Surg Oncol 11:52–58
30. Fletcher AS, Erbas B, Kavanagh AM, Hart S, Rodger A, Gertig DM (2005) Use of hormone replacement therapy (HRT) and survival following breast cancer diagnosis. Breast 14:192–200
31. Rosenberg LU, Granath F, Dickman PW, Einarsdottir K, Wedren S, Persson I, Hall P (2008) Menopausal hormone therapy in

relation to breast cancer characteristics and prognosis: a cohort study. Breast Cancer Res 10:R78
32. Khan HN, Bendall S, Bates T (2007) Is hormone replacement therapy-related breast cancer more favorable? A case–control study. Breast J 13:496–500
33. Chen WY, Hankinson SE, Schnitt SJ, Rosner BA, Holmes MD, Colditz GA (2004) Association of hormone replacement therapy to estrogen and progesterone receptor status in invasive breast carcinoma. Cancer 101:1490–1500
34. Stahlberg C, Pedersen AT, Andersen ZJ, Keiding N, Hundrup YA, Obel EB, Moller S, Rank F, Ottesen B, Lynge E (2004) Breast cancer with different prognostic characteristics developing in Danish women using hormone replacement therapy. Br J Cancer 91:644–650