Review

Etiology of Hormone Receptor–Defined Breast Cancer: A Systematic Review of the Literature

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Abstract

Breast cancers classified by estrogen receptor (ER) and/or progesterone receptor (PR) expression have different clinical, pathologic, and molecular features. We examined existing evidence from the epidemiologic literature as to whether breast cancers stratified by hormone receptor status are also etiologically distinct diseases. Despite limited statistical power and nonstandardized receptor assays, in aggregate, the critically evaluated studies (n = 31) suggest that the etiology of hormone receptor–defined breast cancers may be heterogeneous. Reproduction-related exposures tended to be associated with increased risk of ER-positive but not ER-negative tumors. Nulliparity and delayed childbearing were more consistently associated with increased cancer risk for ER-positive than ER-negative tumors, and early menarche was more consistently associated with ER-positive/PR-positive than ER-negative/PR-negative tumors. Postmenopausal obesity was also more consistently associated with increased risk of hormone receptor–positive than hormone receptor–negative tumors, possibly reflecting increased estrogen synthesis in adipose stores and greater bioavailability. Published data are insufficient to suggest that exogenous estrogen use (oral contraceptives or hormone replacement therapy) increase risk of hormone-sensitive tumors. Risks associated with breast-feeding, alcohol consumption, cigarette smoking, family history of breast cancer, or premenopausal obesity did not differ by receptor status. Large population-based studies of determinants of hormone receptor–defined breast cancers defined using state-of-the-art quantitative immunostaining methods are needed to clarify the role of ER/PR expression in breast cancer etiology. (Cancer Epidemiol Biomarkers Prev 2004;13(10):1558–68)

Introduction

Epidemiologic data, animal models, and *in vitro* studies have shown that reproductive hormones, particularly estrogen, play a critical role in breast cancer etiology (1). Certain established breast cancer risk factors, such as postmenopausal obesity, age at menarche, and use of exogenous hormones, may affect risk by increasing systemic exposure to hormones (2-4), a view that is consistent with prospective studies directly linking higher circulating levels of estradiol to postmenopausal breast cancer (5). In addition to elucidating the systemic effects of hormone-related exposures, progress in breast cancer research will require advances in our understanding of processes that occur within the breast, including hormone synthesis, metabolism, and protein expression.

Despite clinical, pathologic, and molecular evidence that breast cancers are heterogeneous (6), most epidemiologic research to date has viewed breast cancer as a single disease that is associated with a common set of risk factors. Recent interest has focused on assessing risk factors for breast cancers stratified by pathologic features, with the important goal of revealing associations that might otherwise be diluted or masked in analyses in which breast cancer is considered as a single outcome.

Estrogen receptor (ER) and progesterone receptor (PR) are the most widely studied markers in breast tissue. When compared with hormone receptor–negative tumors, hormone receptor–positive breast cancers exhibit stronger clinical responses to hormonal treatment (7), better differentiated morphologic appearance (8), and incidence rates that rise continuously with aging rather than slowing after menopause (9, 10). In contrast to many of the established clinical and pathologic distinctions between ER-defined and PR-defined breast cancers, epidemiologic studies that have compared risk factors for receptor-positive and receptor-negative tumors have led to uncertainty and debate (11). Resolving this controversy will help to clarify whether breast cancers are etiologically heterogeneous. Toward this end, we have critically evaluated published case-control and cohort studies that have compared risk factors for breast cancer, stratified by ER and PR status with two primary goals: (*a*)

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to assess existing evidence that risk factors for breast cancers stratified by ER and PR status differ and (*b*) to highlight aspects of study design, tissue collection, and analysis that should be optimized in future studies. Given the current explosion in tissue biomarker identification and the development and refinement of high-throughput techniques in molecular pathology, identifying approaches that would strengthen future studies is both timely and essential for advancing the field of breast cancer research.

Methods

Scope. We did a computerized bibliographic search of Medline (1966 to February 1, 2004; National Library of Medicine, Bethesda, MD) in the English language to identify controlled epidemiologic studies that assessed the association between risk factors and breast cancer stratified by ER and PR status. Abstracts were reviewed and copies of potentially eligible articles were obtained. We then inspected the bibliographies of the collected articles to identify additional relevant reports, and copies of these articles were also obtained.

Data Abstraction. Two authors abstracted data on study design, method of biomarker assay, and estimates of risk [odds ratios (OR) and relative risks (RR) for case-control and cohort studies, respectively, and their corresponding 95% confidence intervals (CI)] for breast cancer subtypes defined by receptor expression from all potentially relevant articles. Data were recorded in a database specially designed for this project (Microsoft Excel XP). An independent reviewer confirmed data entries.

Results and Risk Factor–Specific Discussion

Description of Studies. We identified 40 relevant published reports of controlled epidemiologic investigations of tissue biomarkers in breast tumors (12-51). Findings from the Nurses' Health Study (12), which were variable estimates from a log incidence model, were not tabulated but rather discussed. Omitted studies reported data on risk factors not summarized by this review (dietary factors, electromagnetic field exposure, blood lipid, and serum organochlorine levels; refs. 43-48) or assessed breast cancer risk only within specific subgroups defined by smoking status or family history of disease (50, 51). We included only the most recent publication (40) of two reports from one case-control study (40, 49) but included multiple publications from other study populations that reported findings for different risk factors or hormone receptor combinations.

This review presents in detail data from 31 published reports (1983-2004) of cohort or case-control studies and 1 randomized clinical trial (Table 1), representing 24 distinct study populations of which 17 were population based and 14 included both premenopausal and postmenopausal women. About half of the studies (13 of 31) assessed <500 cancer cases; only seven studies (representing six distinct populations) evaluated >1,000 cancer cases. Twenty-two studies were conducted in the United States, 3 in Europe, and 2 in Canada, Japan, and Australia. Among the 19 studies that reported stage at diagnosis, ≥75% of patients had invasive carcinomas.

Half of the reports obtained data on hormone receptors for at least 75% of cases enrolled. Assays and thresholds for determining ER and PR status differed across studies, with 23 of 31 studies using nonspecified methods or combinations of dextrose charcoal-coated biochemical methods (DCC) and immunohistochemical assays (IHC). IHC was the sole method used in only three studies. In studies that used a DCC method (11 of 31), the most common threshold for a positive ER or PR result was ≥10 fmol of receptor per milligram of total protein; however, concentrations as low as 3 fmol/mg were used to define positive receptor assays in some investigations. As would be expected (53), the percentage of ER-positive, PR-positive, and ER-positive/PR-positive tumors was generally higher among studies with more older women, with the exception of a recent hospital-based case-control study conducted in Japan. This study reported the lowest proportion of both PR-positive and ER-positive/PR-positive tumors and the third lowest proportion of ER-positive tumors of all investigations reviewed (41). Descriptive studies have found that hormone receptor–positive tumors are less common among Asian as opposed to Western populations (54).

Age at First Birth. Although there was substantial overlap in 95% CIs for risk estimates by hormone receptor status, the increase in risk associated with delayed childbearing was more consistently observed for ER-positive than ER-negative tumors (Table 2). The highest risks were observed among women with later ages at first birth, with risk estimates ranging from 1.4 to 2.6. Data from two centers that participated in the Cancer and Steroid Hormone Study (Washington and Atlanta) differed (38, 39). Data from the Washington site (39), which enrolled predominantly White women, suggested that late age at first birth was more strongly associated with ER-positive as compared with ER-negative tumors, whereas results from the predominantly African American populations enrolled in Atlanta showed the reverse (38). These data may reflect the relatively stronger tendency for African American women to develop ER-negative tumors (55) or a propensity for delayed childbearing to be a stronger risk factor for ER-positive tumors only among White women.

Three of six studies assessing joint ER/PR expression found very modest elevation in hormone receptor–positive but not hormone receptor–negative tumors (23, 29, 32). Older age at first birth did not appreciably elevate risk of breast tumors in the studies that assessed PR expression (35, 41).

Parity. The reduction in breast cancer risk associated with parity was also more consistently observed for ER-positive than ER-negative tumors (Table 3). Although 95% CIs overlapped, the point estimates for ER-positive tumors were <1.0 for seven of eight studies (only two of which were statistically significant). Risk estimates ranged from 0.5 to 0.8, with the greatest reductions noted for multiparous women (36-39). Possible systemic errors in hormone receptor assays (see Discussion) may have attenuated risk estimates and the small size of several studies limited the statistical power of the analyses to find significant differences.

Table 1. Design features of case-control and cohort studies that examine hormone receptors and breast cancer epidemiology

First author (reference)	Publication year	Country (study)	Study population		
			Age (y)*	% Postmenopausal	% Invasive cases
Prospective studies					
Colditz (12)	2004	United States (NHS)	30-55 (BL)	NS	100
Chlebowski (RCT; ref. 13)	2003	United States (WHI)	50-79	100	100
Palmer (14)	2002	United States (DES)	25^{med}	NS	75
Sellers (15, 16)	2002	United States (IWHS)	55-69 (BL)	100	88
Potter (17), Tutera (18) Gapstur (19)	1995	United States (IWHS)	55-69 (BL)	100	94
London (20)	1989	United States (NHS)	30-55 (BL)	NS	NS
Retrospective cohort studies					
Manjer (21)	2001	Sweden	57^{m}	60 (BL)	100
Wohlfahrt (22)	1999	Denmark (DBCG)	45^{m}	NS	100
Population-based case-control studies					
McCredie (23)	2004	Melbourne (Australia)	<40	0	100
Cotterchio (24)	2003	Canada (ON)	25-74	68	100
Li (25)	2003	Western WA	65-79	100	100
Baumgartner (26)	2003	United States (NM)	30-74	63	NS
Zhu (27)	2003	United States (TN)	≥20	57	NS
Althuis (28)	2003	United States (WISH)	20-54	0	85
Britton (29)	2002	United States (WISH)	20-44	12	86
Enger‡ (30, 31)	2000, 1999	United States (LA County)	<41	0	NS
Enger‡ (30, 31)	2000, 1999	United States (LA County)	55-64	100	NS
Huang (32)	2000	United States (CBCS)	20-74	50	100
Morabia (33)	1998	Switzerland	<75	60	100
Nasca (34)	1994	United States (NY)	20-79	63	88
Kreiger (35)	1991	Canada (ON)	20-69	59	NS
Cooper (36)	1989	Australia	20-74	63	NS
Hislop (37)	1986	Canada (BC)	<70	62	NS
Stanford§ (38)	1987	United States (CASH-GA)	20-54	38	NS
McTiernan§ (39)	1986	United States (CASH-WA)	20-54	38	NS
Hospital-based case-control studies					
Yoo (40, 41)	2001, 1997	Japan	25+	NS	100
Hildreth (42)	1983	United States (CT)	45-74	100	NS

NOTE: WHI, Women's Health Initiative; RCT, randomized clinical trial; DES, diethylstilbestrol; IWHS, Iowa Women's Health Study; NHS, Nurses' Health Study; DBCG, Danish Breast Cancer Group; WISH, Women's Interview Study of Health; CBCS, Carolina Breast Cancer Study; CASH, Cancer and Steroid Hormone Study; MR, abstracted from medical records and assay method not specified; fmol/mg, receptor protein concentration per total protein; %, the proportion of stained cells required for positivity; PE, paraffin-embedded tissue; FR, frozen tissue; NS, not specified.

*Age at enrollment, which when specified is age at baseline (BL) for cohort studies. m, mean; med, median age at diagnosis/interview.

†Among total breast cancer cases enrolled, the proportion that had successful completion of tissue analysis for receptor expression.

‡Enger et al. (1999 and 2000) present data from two case-control studies: one of premenopausal women and the other of postmenopausal women.

§Proportion of postmenopausal cases based on study population from all sites (Centers for Disease Control Cancer and Steroid Hormone Study; ref. 52).

Nonetheless, the point estimates suggest that increasing parity may reduce risk of ER-positive breast cancers. Larger studies using optimized methods are needed to clarify this association.

In one of two investigations, parity significantly reduced risk of PR-positive but not PR-negative tumors (35). Equivocal findings in more recent studies assessing joint receptor expression may be attributable to biases related to missing receptor data (17, 41), or the age distribution of the study group (29), many of whom may have been temporarily at higher risk of breast cancer because of a recent birth (56-58).

Age at Menarche. Older age at menarche was not differentially associated with breast cancer risk when defined by ER (27, 35-37, 39, 41) or PR (35) status (Table 4). In contrast, studies stratified by joint receptor expression suggest that ER-positive/PR-positive breast cancer was reduced by older ages at menarche; all studies showed risk estimates of 0.5 to 0.8 compared with younger ages (17, 23, 24, 29, 32, 41). Later menarche did not reduce risk of ER-negative/ER negative tumors in five of these studies (RR ~ 1) and the risk associated with an older age at menarche was similar for ER-positive/PR-positive and ER-negative/PR-negative tumors in one study (29).

Earlier epidemiologic investigations suggested that breast cancer risk associated with a young age at menarche was more pronounced among premenopausal women, a finding most frequently attributed to recall bias (59-61). Three studies examined by this review further stratified their findings by menopausal status (24, 27, 37). A small study of African American women and a large population-based study in Canada reported that the relationship between age at menarche and breast tumors was more marked for premenopausal than postmenopausal women (24, 27). Thus, we cannot discount differences in age distributions as a possible explanation for disparities in findings among studies reviewed.

Postmenopausal Obesity. A consistent association between postmenopausal obesity and ER-positive/PR-positive tumors was identified in three of four studies

Table 1. Design features of case-control and cohort studies that examine hormone receptors and breast cancer epidemiology (Cont'd)

Hormone receptor analysis			% Positive		
Cases with tissue analysis (%)†	Method(s) of detection	Criteria for positivity	ER+	PR+	ER+/PR+
2,096 (74)	DCC, IHC	NS	76	65	61
309 (89)	MR	NS	87	—	—
41 (71)	MR	NS	83	—	—
1,355 (72)	MR	(+) or borderline (+)	82	73	—
610 (65)	MR	(+) or borderline (+)	—	—	68
890 (61)	MR	NS	65	—	—
267 (90)	IHC	NS	70	45	39
6,044 (56)	IHC	≥10 fmol/mg or ≥10%	68	—	—
618 (81)	DCC, IHC	NS	58	65	53
3,276 (87)	DCC, IHC	DCC:≥10 fmol/mg	—	—	56
900 (92)	MR	NS	—	—	72
624 (77)	MR	NS	—	—	46
281 (92)	IHC	NS	54	—	—
1,375 (79)	MR, DCC	(+) or borderline (+), NS	63	61	52
1,212 (78)	MR, DCC	(+) or borderline (+), NS	—	—	51
424 (59)	MR, ~85% DCC	NS	—	—	49
760 (66)	MR, ~85% DCC	NS	—	—	59
783 (91)	MR, primarily IHC	PE range: >0% to >20%; FR range: ≥10-15 fmol/mg	—	—	53
242 (92)	DCC, IHC	≥10 fmol/mg or ≥20%	75	—	—
1,152 (75)	MR	(+): ≥10 fmol/mg; (−): ≤3 fmol/mg; borderline: 4-9 fmol/mg	69	—	—
528 (87)	MR	≥10 fmol/mg	67	55	—
380 (84)	DCC	≥10 fmol/mg	67	—	—
512 (>80)	MR	≥3 fmol/mg or ≥20%	67	—	—
458 (82)	MR, DCC	(+)	45	—	—
240 (73)	MR, DCC	≥7 fmol/mg	60	60	49
455 (39)	DCC, IHC	DCC:≥10 fmol/mg	64	44	39
148 (72)	DCC	≥30 fmol/mg	70	—	—

(one cohort and two case-control) that assessed this relationship (refs. 17, 30, 32; Table 5). Risk estimates among women in the highest compared with the lowest body mass index (BMI) group ranged from 1.5 to 2.5 and increased incrementally with increasing BMI and reached statistical significance in two of the studies. No consistent increase in risk was seen for ER-negative/PR-negative tumors. As would be expected, this association was stronger for case-control designs (30, 32) in which body size was assessed at the time of diagnosis as opposed to assessment in cohort studies, which was generally done at baseline years prior to diagnosis (17). The Iowa Women's Health Study has also shown that postmenopausal obesity was associated with increased risk of hormone receptor–positive breast cancer, whether defined by ER, PR, or joint ER/PR status (15, 17). Findings from the Nurses' Health Study, which evaluated ER status after adjusting for PR status and vice versa, suggest that PR (not ER) expression is independently associated with BMI after menopause (12).

Exogenous Hormone Use

Oral Contraceptives. With the exception of the Women's Interview Study of Health, which was the only study to report a statistically significant increase (28), we found very modest evidence that ever use of combination oral contraceptives was more strongly associated with ER-negative than ER-positive tumor subtypes (Table 6). Althuis et al. (28), Stanford et al. (38), and Cooper et al. (36) reported suggestions of a similar differential effect; however, the remaining studies that assessed either ER expression alone or joint receptor expression were inconsistent (23, 24, 29, 32, 33, 39). Although the risk associated with oral contraceptives is most strongly related to recent use, a relationship that is most marked among women younger than 35 years (62), time since last use was evaluated in only three studies (24, 28, 39). As expected, recent use was more strongly associated with breast cancer risk (than ever use) in two of these investigations. Nonoptimal assessment of oral contraceptive use

Table 2. Age at first birth and breast cancer risk stratified by hormone receptor expression

First author (reference)	Country (study)	Cases (*n*)	Age at first birth (*y*)		Risk estimate (95% CI)*	
			Reference group	Age		
					ER+	ER−
McTiernan† (39)	United States (CASH-WA)	240	<20	20-24	1.0 (0.5-1.9)	0.2 (0.1-5.0)
				25-29	1.5 (0.7-3.1)	1.0 (0.4-1.9)
				30+	2.6 (1.1-6.6)	0.8 (0.3-2.4)
Althuis‡ (28)	United States (WISH)	1,375	<20	20-24	1.1 (0.8-1.6)	0.9 (0.6-1.3)
				25-29	1.4 (1.0-2.0)	0.9 (0.6-1.3)
				30+	2.0 (1.4-2.8)	1.1 (0.7-1.7)
				Nulliparous	1.6 (1.1-2.3)	1.1 (0.7-1.6)
Cooper (36)	Australia	380	<20	20-24	1.1 (0.5-2.1)	2.4 (1.0-5.9)
				25-29	1.3 (0.6-2.5)	1.2 (0.5-2.8)
				30+	1.6 (0.7-3.5)	1.3 (0.4-4.4)
				Nulliparous	1.4 (0.7-3.1)	1.7 (0.6-5.1)
Stanford† (38)	United States (CASH-GA)	458	<20	20-28	1.2 (0.7-1.9)	1.0 (0.6-1.5)
				29+	1.2 (0.5-2.8)	1.7 (0.8-3.7)
Kreiger (35)	Canada (ON)	528	<21	21-30	0.7 (0.5-1.1)	0.7 (0.4-1.4)
				31+	0.9 (0.5-1.6)	0.6 (0.2-1.3)
				Nulliparous	1.2 (0.7-2.0)	0.8 (0.3-1.7)
Wohlfahrt† (22)	Denmark (DBCG)	6,044	20-24	12-19	1.0 (0.9-1.1)	1.0 (0.9-1.2)
				25-29	1.2 (1.1-1.3)	1.1 (1.0-1.2)
				30-34	1.3 (1.1-1.4)	1.3 (1.0-1.5)
				35+	1.6 (1.3-2.0)	0.9 (0.6-1.4)
Hislop (37)	Canada (BC)	512	<25	25-29	1.2	0.9
				30+	1.4	1.0
				Nulliparous	1.6 (1.3-2.1)§	0.9 (0.6-1.4)§
Yoo† (41)	Japan	455	Continuous	Per 5 y older	1.2 (1.0-1.5)	1.1 (0.9-1.5)
Hildreth† (42)	United States	148	Continuous	Per 10 y older	1.5 (0.9-2.4)	0.7 (0.3-1.4)
					PR+	PR−
Kreiger (35)	Canada (ON)	528	<21	21-30	0.7 (0.4-1.1)	0.8 (0.4-1.3)
				31+	0.9 (0.5-1.6)	0.6 (0.3-1.2)
				Nulliparous	1.3 (0.7-2.1)	0.8 (0.4-1.4)
Yoo† (41)	Japan	455	Continuous	Per 5 y older	1.1 (0.9-1.4)	1.2 (1.0-1.5)
					ER+/PR+	ER−/PR−
Cotterchio† (24)	Canada (ON)	3,276	<24	*Premenopause*		
				24-27	1.2 (0.8-1.8)	0.9 (0.5-1.5)
				28+	1.1 (0.7-1.6)	1.0 (0.6-1.7)
				Nulliparous	1.8 (1.1-2.9)	0.9 (0.5-1.7)
				Postmenopause		
				24-27	1.2 (1.0-1.5)	1.3 (1.0-1.8)
				28+	1.6 (1.3-2.1)	1.3 (0.9-1.9)
				Nulliparous	1.5 (1.1-2.0)	1.5 (1.0-2.3)
Britton† (29)	United States (WISH)	1,212	<24.4	24.4+	1.2 (0.9-1.6)	1.0 (0.8-1.4)
McCredie† (23)	Melbourne (Australia)	618	<25	25+	1.7 (1.1-2.5)	0.9 (0.6-1.4)
Huang† (32)	United States (CBCS)	783	<26	26+	1.3 (0.9-1.8)	0.8 (0.5-1.3)
				Nulliparous	1.4 (0.9-2.2)	0.9 (0.6-1.5)
Potter† (17)	United States (IWHS)	610	<30	30+	1.8 (1.2-2.6)	1.7 (0.8-3.9)
Yoo† (41)	Japan	455	Continuous	Per 5 y older	1.2 (0.9-1.5)	1.2 (0.9-1.6)

*ORs were the reported risk estimates for case-control studies and RRs for cohort designs.
† Adjusted for (*a*) number of full-term births/live births, (*b*) breast-feeding, or (*c*) both.
‡ Among premenopausal women ages 35-54 years.
§ Age-adjusted only.

(29, 32, 33, 36, 38) and inclusion of older women (32, 33, 36, 38, 39) may have diluted the strength of the findings across studies.

Hormone Replacement Therapy. Most investigations of hormone replacement therapy (HRT) stratified by hormone receptor status failed to report significant increases in breast cancer risk (17, 24, 32, 36, 38, 42). The Nurses' Health Study did not find an increase among current users but reported a stronger association of past use of postmenopausal hormones with ER-positive than ER-negative tumors (12). Two recent studies that have examined the risk associated with specific regimens of HRT [combined HRT (CHRT) or estrogen replacement therapy] and receptor-defined breast cancer have yielded statistically significant but conflicting results (13, 25). One study found that any use of CHRT was associated with a 2-fold increased risk of ER-positive/PR-positive tumors only, with higher risks for current long-term use (OR, 2.9; 95% CI, 1.8-4.8; ref. 25). The other found that CHRT was associated with similarly elevated risk for receptor-positive and receptor-negative tumors; data for estrogen replacement therapy are not yet available from this study (13). Potential biases related to both study

designs (i.e., recall for the case-control study and the nonrepresentative population of women who enroll in clinical trials) may explain the disparate findings and more studies are needed for clarity.

Diethylstilbestrol Exposure In utero. Breast cancer incidence in a cohort of diethylstilbestrol-exposed daughters and unexposed women of the same ages reported that excess risk associated with diethylstilbestrol exposure pertained exclusively to ER-positive cases (14). This finding was of borderline significance and based on receptor data for only half of breast cancers diagnosed in the cohort.

Factors Similarly Associated with Hormone Receptor–Defined Breast Cancer. In aggregate, the published data do not suggest that breast cancer defined by either ER or PR expression is differentially associated with any of the following risk factors: breast-feeding (24, 29, 32, 36, 39, 41, 42), alcohol consumption (12, 16, 17, 19, 24, 26, 29-32, 34, 36, 39, 41), cigarette smoking (20, 21, 24, 29, 32, 33, 36, 38, 39, 41), first-degree relative with breast cancer (12, 17, 18, 24, 29, 33, 35-39, 41), or premenopausal obesity (12, 24, 30, 32, 40). Risk estimates for factors similarly associated with hormone receptor–defined breast cancers have been tabulated and are available in an online appendix.

Implications for Breast Cancer Etiology: Summary and Conclusions

Our critical review of 31 epidemiologic investigations revealed possible disparate risk factor profiles for breast tumor subtypes defined by ER and PR status, suggesting that they may represent etiologically distinct diseases. Reproductive factors and postmenopausal obesity seem to increase risk only of hormone receptor–positive breast tumors. Although the absolute differences in risk of hormone receptor–defined breast cancers associated with these factors were relatively modest and there was overlap in 95% CIs for estimates of risk for hormone receptor–positive and hormone receptor–negative tumors, the findings were consistent despite considerable variation in study populations, size, designs, and

Table 3. Parity and breast cancer risk stratified by hormone receptor expression

First author (reference)	Country (study)	Cases (*n*)	Births (*n*)*	Risk estimate (95% CI)†	
				ER+	ER−
Wohlfahrt (22)	Denmark (DBCG)	6,044	1+	0.8 (0.7-0.8)	0.9 (0.8-1.0)
Hildreth (42)	United States	148	1+	0.6 (0.3-1.1)	2.5 (0.8-10.0)
Cooper (36)	Australia	380	1	1.4 (0.7-2.7)	1.3 (0.5-3.4)
			2	0.8 (0.5-1.4)	0.8 (0.4-1.9)
			3+	0.8 (0.5-1.4)	1.0 (0.4-2.3)
Hislop (37)	Canada (BC)	512	1-2	0.8 (0.6-1.0)‡	0.9 (0.6-1.4)‡
			3+	0.7 (0.6-1.0)‡	1.3 (0.9-2.0)‡
McTiernan (39)	United States (CASH-WA)	240	1-2	0.8	1.9
			3+	0.6 (0.3-1.5)	1.4 (0.6-3.6)
Stanford (38)	United States (CASH-GA)	458	1-2	1.0 (0.6-1.6)‡	0.9 (0.6-1.5)‡
			3-4	0.7 (0.4-1.2)‡	0.8 (0.5-1.3)‡
			5+	0.5 (0.2-1.0)‡	1.0 (0.5-1.9)‡
Kreiger (35)	Canada (ON)	528	1-3	0.7 (0.5-0.9)	0.9 (0.5-1.6)
			4+	0.7 (0.4-1.1)	1.4 (0.6-3.0)
Yoo (41)	Japan	455	Per 1 child	1.0 (0.8-1.1)	0.9 (0.8-1.2)
				PR+	PR−
Kreiger (35)	Canada (ON)	528	1-3	0.6 (0.4-0.9)	0.9 (0.6-1.5)
			4+	0.5 (0.3-0.8)	1.6 (0.9-3.1)
Yoo (41)	Japan	455	Per 1 child	0.9 (0.7-1.1)	1.0 (0.9-1.2)
				ER+/PR+	ER−/PR−
McCredie (23)	Melbourne (Australia)	618	1	1.1 (0.7-1.7)	1.3 (0.8-2.3)
			2	1.0 (0.7-1.5)	1.0 (0.6-1.7)
			3+	1.0 (0.5-1.2)	0.8 (0.4-1.3)
Cotterchio (24)	Canada (ON)	3,276	*Premenopause*		
			1	0.6 (0.4-1.1)	1.0 (0.5-2.0)
			2	0.7 (0.4-1.0)	1.1 (0.6-2.0)
			3+	0.4 (0.3-0.8)	0.9 (0.5-1.8)
			Postmenopause		
			1	1.0 (0.7-1.4)	0.9 (0.6-1.6)
			2	0.8 (0.6-1.2)	0.7 (0.5-1.2)
			3+	0.7 (0.5-1.0)	0.7 (0.5-1.1)
Britton (29)	United States (WISH)	1,212	1+	0.8 (0.6-1.1)	0.8 (0.5-1.2)
Potter (17)	United States (IWHS)	610	1-2	0.8 (0.5-1.1)	2.1 (0.6-6.9)
			3+	0.8 (0.5-1.1)	2.2 (0.7-7.2)
Yoo (41)	Japan	455	Per 1 child	1.0 (0.8-1.2)	1.0 (0.8-1.2)

NOTE: Adjustment for other reproductive variables was sometimes unclear. Hildreth et al., McTiernan et al., and Yoo et al. adjusted for age at first birth and breast-feeding, assigning nulliparous women a value of zero in the model.
*Reference group is nulliparous women.
† ORs were the reported risk estimates for case-control studies and RRs for cohort designs.
‡ Age-adjusted only.

Table 4. Age at menarche and breast cancer risk stratified by hormone receptor expression

First author (reference)	Country (study)	Cases (*n*)	Age at menarche (y)		Risk estimate (95% CI)*	
			Reference group	Age category		
					ER+	ER−
Kreiger (35)	Canada (ON)	528	<12	12-14	0.8 (0.5-1.1)	0.9 (0.5-1.6)
				15+	0.8 (0.5-1.3)	0.7 (0.3-1.5)
Zhu† (27)	United States (TN)	281	<13	13+	1.0 (0.6-1.6)	1.2 (0.7-2.1)
Cooper (36)	Australia	380	<13	13	0.9 (0.6-1.5)	0.9 (0.6-1.7)
				14+	1.0 (0.6-2.1)	0.8 (0.4-1.4)
Hislop (37)	Canada (BC)	512	<13	13	0.9 (0.7-1.1)	0.9 (0.7-1.2)
				14+	1.0 (0.8-1.2)	1.1 (0.8-1.4)
McTiernan (39)	United States (CASH-WA)	240	<13	13+	1.3 (0.8-1.9)	1.8 (1.1-3.0)
Yoo (41)	Japan	455	Per 2 y older	Continuous	1.0 (0.9-1.2)	1.1 (0.9-1.3)
					PR+	PR−
Kreiger (35)	Canada (ON)	528	<12	12-14	0.7 (0.5-1.1)	0.9 (0.6-1.5)
				15+	0.8 (0.5-1.3)	0.7 (0.4-1.4)
Yoo (41)	Japan	455	Per 2 y older	Continuous	0.8 (0.7-1.0)	1.2 (1.0-1.4)
					ER+/PR+	ER−/PR−
Cotterchio (24)	Canada (ON)	3,276	<12	*Premenopause*		
				12	0.6 (0.4-0.9)	1.1 (0.6-1.9)
				13	0.5 (0.3-0.8)	1.1 (0.6-1.8)
				14+	0.5 (0.3-0.8)	1.1 (0.6-2.0)
				Postmenopause		
				12	1.3 (1.0-1.7)	1.0 (0.7-1.5)
				13	1.2 (0.9-1.5)	1.0 (0.7-1.4)
				14+	0.8 (0.6-1.1)	0.9 (0.6-1.4)
Huang (32)	United States (CBCS)	783	<12	12+	0.7 (0.5-0.9)	0.9 (0.7-1.4)
McCredie (23)	Melbourne (Australia)	618	<13	13+	0.8 (0.6-1.1)	0.9 (0.5-1.8)
Britton (29)	United States (WISH)	1,212	<13	13+	0.8 (0.6-0.9)	0.8 (0.6-1.0)
Potter (17)	United States (IWHS)	610	<13	13+	0.7 (0.6-0.9)	1.1 (0.7-1.7)
Yoo (41)	Japan	455	Per 2 y older	Continuous	0.8 (0.7-1.0)	1.1 (0.9-1.4)

NOTE: Table excludes Morabia et al. (33), who found that an older age at menarche similarly reduced the risk of both ER+ and ER− breast cancers; however, ORs were not presented in the article.

*ORs were the reported risk estimates for case-control studies and RRs for cohort designs.

† Among African American women.

receptor assays. Therefore, in aggregate, these studies suggest that assessing risk factors for breast cancer subtypes defined by receptor status, histopathologic appearance, and other biomarkers may be important for future epidemiologic research.

In the majority of studies reviewed, increased risk associated with reproductive factors (delayed childbearing, nulliparity, and early menarche) seemed to be restricted to hormone receptor–positive tumors, with no appreciable elevation in hormone receptor–negative cancers. These exposures have been postulated to confer risk by increasing systemic exposure to cycling reproductive hormones (2, 63). Increased risk of hormone receptor–positive tumors was also associated with postmenopausal obesity, which probably increases estrogen exposure via different mechanisms (4). In adipose tissue, obesity is associated with increased aromatization of circulating androgens to estrogens and reduced levels of sex hormone binding globulin, thereby increasing both total and bioavailable estrogens (64). Although many factors have been shown to contribute to elevated systemic levels of estrogens, a relationship between high serum levels and the development of hormone receptor–positive tumors has not been established (65). In addition, the effect of hormone-related risk factors on hormone content within the breast is unknown. Limited data suggest that hormone levels in the breast may far exceed concentrations in serum, especially among postmenopausal women (66). Therefore, studies designed to measure both estrogen and progesterone levels in breast tissue and identify the determinants of these levels are needed.

It is unclear whether exogenous hormone use, which increase endogenous estrogen levels, differentially increases risk of hormone-sensitive tumors. Although the demonstration of a link between postmenopausal HRT and breast cancer risk supports the role of reproductive hormones in breast cancer etiology (67), only one study reported that CHRT-associated risk was more marked for receptor-positive than receptor-negative tumors (25). Large studies of postmenopausal women capable of detecting modest increases in risk and employing improved assessments of formulations, total exposure, and temporal patterns of use are needed. If anything, oral contraceptive use was more consistently associated with increased risk for ER-negative tumors, with less of an affect on ER-positive cancers. ER-negative tumors are more often diagnosed prior to menopause, a period characterized by cyclic levels of hormones and periods of sustained elevation during pregnancy. In contrast to a factor such as postmenopausal obesity, which may produce mainly sustained high levels of estrogen, understanding hormonal exposures and their possible relationship to premenopausal breast cancer risk seems exceedingly complex and poorly understood. Nonetheless, the higher frequency

of ER-negative tumors among women who are young (52), African American (55), or BRCA1 carriers (68) suggests an etiologic role for genetic factors in these tumors and raises the possibility that the association between oral contraceptive use and receptor-negative tumors may reflect residual confounding related to age at diagnosis.

A positive family history of breast cancer and alcohol consumption seem to increase risk for ER-positive and negative tumors similarly. The increased risk associated with a positive family history may reflect many different heritable factors, some of which affect risk for ER-positive tumors and others for ER-negative tumors. Identification of families with multiple affected members whose tumors show concordant receptor expression may permit the elucidation of specific mechanisms that distinguish receptor-positive from receptor-negative cancers. Similarly, the diverse and complex biochemical effects of alcohol consumption could result in risk elevations for both receptor categories.

The lack of associations between smoking and premenopausal obesity with tumor receptor status might be predictable; the former may be unrelated to risk (69) and the latter is only modestly protective (70). Similarly, detection of associations between breast-feeding and receptor status is limited by the modest risks associated with short-term lactation, which predominates in developed nations (71). Although the lack of statistically significant findings pervasive among these studies may be real, they may also be a result of low power due to the small numbers of cases within strata defined by hormone receptor status, particularly among hormone receptor–negative tumors that constitute a minority of breast cancers diagnosed.

Use of nonstandardized, suboptimal hormone receptor assays in reported studies may have spuriously weakened or obscured associations between risk factors and breast cancer subtypes. Reported studies have generally relied on results of clinical assays that were done to predict response to tamoxifen therapy rather than to investigate breast cancer etiology. A recent survey of immunostaining procedures for ER expression in the United States found that over eight different IHC reagent antibodies were currently in use and that staining protocols, methods of assessment, and reporting varied widely (72). Different techniques for measuring ER and PR have specific limitations (1). For example, biochemical assays can only be done on tumors that are large enough to be grossly identified and sampled for testing without compromising the pathologic diagnosis, suggesting that small cancers may have been excluded in studies that have used these assays. Finally, ER and PR results have been scored as ''positive'' and ''negative'' although receptor protein concentration (in biochemical assays) and the percentage of cells stained and staining intensity (in IHC assays) range widely.

Competing proposals to explain the origin of ER-negative and ER-positive tumors include (*a*) the existence of two independent pathways of carcinogenesis and (*b*) the development of all tumors through a single pathway resulting in neoplasms that initially are ER positive but may subsequently be transformed into ER-negative tumors via epigenetic and/or genetic events (73). The tendency of most breast cancers to maintain their original receptor status over time, even following tamoxifen treatment (74), the distinctive age-specific incidence patterns for ER-negative and ER-positive tumors (9, 10),

Table 5. Postmenopausal obesity and breast cancer risk stratified by hormone receptor expression

First author (reference)	Country (study)	Cases (*n*)	BMI (kg/m^2)*		Risk estimate (95% CI)†	
			Reference group	BMI category		
					ER+	ER−
Sellers (15)	United States (IWHS)	1,355	<22.90	22.90-25.04	1.3 (1.0-1.6)	1.4 (0.8-2.2)
				25.05-27.43	1.4 (1.1-1.7)	1.4 (0.9-2.3)
				27.44-30.69	1.8 (1.4-2.2)	2.0 (1.2-3.2)
				30.70+	2.0 (1.6-2.5)	1.4 (0.8-2.4)
Yoo (40)	Japan	455	Continuous	Per 1 kg/m^2	1.09 (1.05-1.13)	1.05 (0.99-1.12)
					PR+	PR−
Sellers (15)	United States (IWHS)	1,355	<22.90	22.90-25.04	1.3 (1.0-1.7)	1.1 (0.8-1.6)
				25.05-27.43	1.5 (1.2-1.9)	1.0 (0.7-1.5)
				27.44-30.69	2.0 (1.6-2.5)	1.5 (1.0-2.1)
				30.70+	2.2 (1.7-2.9)	1.0 (0.6-1.5)
Yoo (40)	Japan	455	Continuous	Per 1 kg/m^2	1.09 (1.04-1.14)	1.07 (1.02-1.11)
					ER+/PR+	ER−/PR−
Enger (30)	United States (LA County)	760	<21.7	21.7-23.6	1.4 (1.0-1.9)	1.2 (0.7-2.0)
				23.7-27.0	1.8 (1.3-2.5)	0.8 (0.5-1.4)
				27.1+	2.5 (1.7-3.5)	1.2 (0.7-2.1)
Huang (32)	United States (CBCS)	783	<23	23-31	1.1 (0.7-1.8)	1.0 (0.6-1.9)
				31+	1.6 (0.9-3.0)	0.8 (0.4-1.7)
Cotterchio (24)	Canada (ON)	1,867	20-25	<20	0.7 (0.4-1.2)	1.3 (0.7-2.5)
				25.1-27	1.1 (0.8-1.4)	1.1 (0.7-1.6)
				27.1+	1.6 (1.3-2.0)	1.5 (1.1-2.0)
Potter (17)	United States (IWHS)	610	<30	30+	1.5 (1.1-1.9)	0.8 (0.8-2.8)

*Current or baseline BMI (kg/m^2), except for Enger et al. and Huang et al., who report BMI 1 year prior to interview.
†ORs were the reported risk estimates for case-control studies and RRs for cohort designs.

Table 6. Exogenous hormone use and breast cancer risk stratified by hormone receptor expression

First author (reference)	Country (study)	Cases (*n*)	Risk estimate (95% CI)*	
Combination oral contraceptives				
			ER+	ER−
Althuis† (28)	United States (WISH)	1,375	1.6 (0.9-2.8)	3.1 (1.6-5.9)
Stanford (38)	United States (CASH-GA)	458	0.8 (0.6-1.2)	1.2 (0.8-1.8)
McTiernan (39)	United States (CASH-WA)	240	1.2 (0.7-1.9)	0.8 (0.5-1.4)
Cooper (36)	Australia	380	0.9 (0.5-1.5)	1.3 (0.7-2.6)
			ER+/PR+	ER−/PR−
Cotterchio (24)	Canada (ON)	3,276	0.9 (0.6-1.2)	1.2 (0.8-1.9)
McCredie (23)	Melbourne (Australia)	618	1.1 (0.7-1.9)	0.9 (0.5-1.6)
Britton (29)	United States (WISH)	1,212	1.2 (0.9-1.5)	1.5 (1.0-2.1)
Huang (32)	United States (CBCS)	783	1.5 (0.8-2.7)	1.1 (0.6-1.9)
Hormone Replacement Therapy				
			ER+	ER−
Chlebowski (13)	WHI	309	1.4 (1.1-1.7)^{CHRT}	1.5 (0.8-2.9)^{CHRT}
Cooper (36)	Australia	380	0.9 (0.5-1.4)^{NS}	1.8 (0.5-2.2)^{NS}
Hildreth‡ (42)	United States (CT)	148	0.9 (0.7-1.2)^{NS}	1.3 (0.9-1.8)^{NS}
Stanford (38)	United States (CASH-GA)	458	1.0 (0.7-1.4)^{NS}	1.0 (0.7-1.3)^{NS}
			PR+	PR−
Chlebowski (13)	WHI	309	1.5 (1.1-2.0)^{CHRT}	1.2 (0.8-1.8)^{CHRT}
			ER+/PR+	ER−/PR−
Li (25)	Western WA	900	1.1 (0.8-1.5)^{ERT} 2.0 (1.5-2.7)^{CHRT}	1.0 (0.6-1.7)^{ERT} 0.9 (0.5-1.8)^{CHRT}
Huang (32)	United States (CBCS)	783	0.9 (0.6-1.2)^{NS}	0.6 (0.4-0.9)^{NS}
Potter (17)	IWHS	610	1.1 (0.9-1.3)^{NS}	1.1 (0.7-1.8)^{NS}
DES exposure *in utero*				
			ER+	ER−
Palmer (14)	United States (DES)	41	1.9 (0.8-4.5)	0.4 (0.1-1.9)

NOTE: Table excludes Morabia et al. (33), who found that risk associated with oral contraceptive use was similarly elevated for ER+ and ER− breast cancers; however, ORs were not presented in the article.

*Ever-users compared with never-users. ERT, estrogen replacement therapy. CHRT, combination hormone replacement therapy; NS, formulation not specified. ORs were the reported risk estimates for case-control studies and RRs for cohort designs.

† Among women ages 20-34 years. No significant association was found among women ages 35-54 years: ER+, OR, 1.0 (0.8-1.3); ER−, OR, 1.2 (0.9-1.6).

‡ HRT modeled as a continuous variable; risk was estimated for every 50 mg/mo of use.

and our review suggest either that the etiology of receptor-positive and receptor-negative cancers are distinct or that they diverge early in the pathogenesis of these tumors. However, the fact that stratification of breast cancers by hormone receptor status reveals etiologic and molecular diversity does not guarantee that this heterogeneity is produced by differences in hormonal exposures. ER-positive and ER-negative tumors differ in the expression of many genes that do not seem to be controlled by hormones (75). Additionally, many hormones affect breast tissue in addition to estrogen and progesterone, and breast cancer risk may reflect the integrated effects of these exposures over time.

Additional studies are required to elucidate differences in breast cancer risk factors by receptor status. Although some investigators contend that joint expression of ER and PR is the hallmark of a ''functional'' ER and therefore the most appropriate comparison, the majority of studies to date have focused only on ER status. In addition to assessing ER and PR status, independently and jointly, future studies need to establish the magnitude and direction of the relationship between risk factors and breast cancer subtypes and to formally test whether these groups are different, which was done in surprisingly few of the studies we summarized. This will require rigorous epidemiologic designs rather than case series, which dominated early work in this field and is not summarized by this review (76-92).

Future etiologic studies of breast cancer should stratify analyses by histopathologic type and molecular characteristics of the tumors. Important initial studies include a population-based analysis of risk factors by hormone receptor status using state-of-the-art quantitative immunostaining methods followed by expansion of this work to include ER-β and receptor variants. Comprehensive investigations that correlate serum and tissue hormones with risk factors and hormone receptor expression and, ultimately, with molecular profiles may be possible in the future.

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