Relationship between Hormonal, Reproductive, Anthropometric, and Lifestyle Factors and Risk of Lobular and Ductal Breast Cancer

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A dissertation submitted in partial fulfillment of the requirements for the degree of

Doctor of Philosophy

University of Washington

2002

Program Authorized to Offer Degree:

Public Health & Community Medicine - Epidemiology

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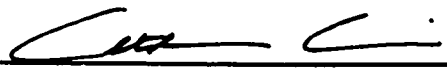
Signature 

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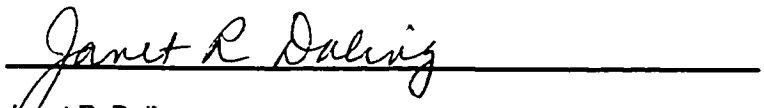

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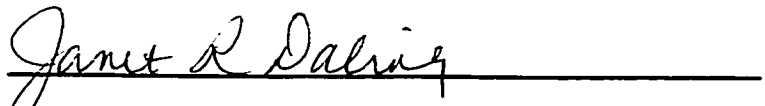

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ABSTRACT

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Christopher I-Fu Li

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Public Health & Community Medicine - Epidemiology

Background:

Recent studies report that use of combined estrogen and progestin hormone replacement therapy (CHRT) increases risk of invasive lobular breast carcinomas (ILC), but has a more modest impact on invasive ductal carcinoma (IDC) risk. However, data on CHRT use for long durations and on risks associated with different CHRT regimens are lacking. Further, though there is evidence that ILC is more hormonally responsive than IDC, few studies have evaluated associations between ILC incidence and other hormonally related breast cancer risk factors, including reproductive, anthropometric, and lifestyle characteristics.

Methods:

A population-based case-control study of women 65-79 years of age was conducted in western Washington State. The responses of 975 women diagnosed with breast cancer during 1997-1999 were compared to those of 1,007 controls. Associations between use of different hormone replacement regimens, and various reproductive, anthropometric, and lifestyle factors, and risks of IDC (n=656) and ILC (n=196) were evaluated using polytomous regression.

Results:

Users of unopposed estrogen, even for ≥25 years, did not have an elevated risk of breast cancer. Ever users of CHRT had elevated risks of lobular, ductal, and breast carcinomas of all histologic types (odds ratio (OR)=2.6, OR=1.6, and OR=1.7, respectively). Five or more years of oral contraceptive use and use of alcohol also increased risk of ILC, but not IDC. Alternatively, earlier age at menarche, later age at menopause, and obesity were more strongly associated with IDC risk.

Conclusions:

We find that long-term use of CHRT is more strongly associated with breast cancer risk than is ERT use, and that CHRT use increases ILC risk to a greater magnitude than it does IDC risk. Alternatively, certain reproductive and anthropometric factors were associated with elevated risks of IDC, but not ILC. Our results suggest that endogenous hormone levels are more strongly related to IDC risk than to ILC risk, while exogenous hormones are more strongly related to ILC risk than to IDC risk. Given the known heterogeneity of breast cancer, differences in etiologic associations are not unexpected. Identification of risk factors related to different histologic types of breast cancer will likely further our understanding of breast cancer etiology.

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ACKNOWLEDGEMENTS

I would like to thank Janet Daling for her invaluable mentorship since I first came to Fred Hutchinson in 1996. She inspired me to study epidemiology and to ultimately pursue a career in cancer research. I am especially grateful for her incredible knowledge, insight, and encouragement throughout this and all of the other projects I have worked on with her. I could not imagine finding a mentor who is more supportive and caring than she is.

I would also like to thank Kathi Malone for all of her help since I first came to Seattle, and particularly for her thoughts and assistance throughout my graduate work; Noel Weiss for his thoughtful, critical, and rapid reviews of my manuscripts, and for his advice as my career in epidemiology has progressed; and Peggy Porter for her insight and support of my work.

I would also like to thank the Weiss-Daling staff, without whom the PACE and SHARE studies would not have been possible. In particular, the high quality of the data collected in these studies is a result of the outstanding study management provided by Diane Setterholm and Rachel Remler, the support provided by Vickie Blakey, and the determination of all of the interviewers who worked on these studies. I also benefited greatly from the biostatistical support provided by Mei Chen, Kara Haugen, and Lynda Voigt.

Finally, I would like to thank my family and friends, especially Emily, my parents, and Steph, for all of their love and support.

DEDICATION

For my parents, Jonathan and Sara Antonia Li, for their guidance and unconditional love and support.

CHAPTER 1:

The relationship between long-term use of hormone replacement therapy and risk of breast cancer among women 65-79 years of age

ABSTRACT

Background: Women who use combined estrogen and progestin hormone replacement therapy (CHRT) have been observed to be at an increased risk of breast cancer, particularly for tumors with a lobular histology. However, there is a lack of data on women who have used CHRT for very long durations (e.g. ≥15 years), and on the risk associated with different forms of CHRT.

Methods: A population-based case-control study of women 65-79 years of age was conducted in western Washington State. The responses of 975 women diagnosed with invasive breast cancer from 1997-1999 were compared to those of 1,007 controls. Associations between use of different hormone replacement regimens and risks of lobular (n=196), ductal (n=656), and all histologic types of breast cancer were evaluated using polytomous regression.

Results: Users of unopposed estrogen replacement therapy (ERT), even for ≥25 years, did not have an elevated risk of breast cancer, while users of CHRT for ≥5 years had greater than 2.0-fold increases in their risk of breast cancer. Some differences by histology were observed as ever users of CHRT had a 2.6-fold (95% CI: 1.7-4.0) increased risk of ILC and a 1.6-fold (95% CI: 1.2-2.1) increased risk of IDC. Associations of similar magnitudes were seen among users of both sequential and continuous CHRT.

Conclusions: Use of ERT, even for durations of ≥25 years, does not appear to increase breast cancer risk among women 65-79 years of age. However, use of CHRT, both sequential and continuous regimens, for ≥5 and ≥15 years does increase breast cancer risk, though it appears to increase risk of ILC to a greater magnitude than it does IDC.

INTRODUCTION

The Collaborative Group on Hormonal Factors in Breast Cancer reported that current users of combined estrogen and progestin hormone replacement therapy (CHRT) for 5 years or longer have a 53% increase in breast cancer risk.[1] Similarly, the Women's Health Initiative (WHI), a randomized controlled trial, found that CHRT use is associated with a 26% increase in breast cancer risk after 5.2 years of follow-up.[2] However, few studies have evaluated the possible effect of very long durations of CHRT use on breast cancer risk, or the possible differential influence of continuous versus interrupted use of the progestin component of CHRT.

Five recent studies have reported that CHRT use is associated with a 2.0 to 3.9-fold increased risk of invasive lobular carcinoma (ILC), the second most common histologic type of breast cancer, but generally not with the most common histologic type, invasive ductal carcinoma (IDC).[3-7] In the three studies that evaluated duration of use, each found that ILC risk increased as duration of CHRT use increased.[5-7] However, these reports have been limited by relatively small numbers of women with lobular cancer, and none have been able to evaluate the possible impact of very long durations of hormone replacement therapy (HRT). Distinguishing between breast carcinomas by histology is clinically important because ILCs are more likely to be hormone receptor positive[8] and to have a better prognosis than IDCs,[9] though they are also more difficult to detect by mammography and clinical breast exams.[10] Additionally, ILC incidence rates have increased steadily since 1977 among women 50 years of age and older in the United States, while IDC incidence rates have remained essentially constant since 1987.[11]

Using data from a population-based case-control study of breast cancer in older women, we assessed the relationship between HRT and different histologic types of invasive breast cancer focusing on specific hormone regimens, as well as on recency and duration of use.

METHODS

We conducted a population-based case-control study of women 65-79 years of age living in the three county Seattle-Puget Sound metropolitan area. Study interviewers conducted in-person interviews on all subjects.

Cases

Women aged 65-79 years with no prior history of *in-situ* or invasive breast cancer when diagnosed with invasive breast cancer between April 1, 1997 and May 31, 1999, were eligible as cases. The Cancer Surveillance System (CSS), the population-based tumor registry that serves the Seattle-Puget Sound region of Washington State and participates in the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute, was used to identify cases. In order to be eligible for the study, cases had to live in King, Pierce, or Snohomish counties and have a Health Care Financing Administration (HCFA) record, since these records were used to identify controls. Of the 1,210 eligible cases identified, 975 (80.6%) were interviewed. Of the 235 cases who were not interviewed, 73% refused to be interviewed, 19% died before an interview could be conducted, 4% moved away from the area, and the physicians treating 4% of cases refused to allow contact with their patients. Information on tumor histology was ascertained from CSS, which abstracts data on tumor characteristics from medical records and pathology reports from institutions serving the area. CSS classifies histology using International Classification of Diseases for Oncology (ICD-O) codes. We divided cases into two groups, with codes 8520 and 8522 used to define the 196 ILC cases and code 8500 used to define the 656 IDC cases.

Controls

HCFA records were used to identify women from the general population of female residents of King, Pierce, and Snohomish counties who were the same ages as cases to serve as controls. Of the 1,365 eligible women selected as controls, 1,007 (73.8%) were interviewed. Of the 358 controls who were not interviewed, 84% refused to be interviewed, 7% died after

selection but before they could be interviewed, 6% moved away from the area, and 4% we were unable to locate.

Data Collection

The study protocol was approved by the Fred Hutchinson Cancer Research Center Institutional Review Board, and informed consent was obtained from all study subjects. Both cases and controls were interviewed in-person and were asked about menstrual, contraceptive and reproductive histories, body size, and medical history, including family history of cancer. Demographic data and information on smoking and alcohol use were also collected. Additionally, detailed histories of all episodes of HRT use, including beginning and ending dates, total duration, brand, dose, and pattern of use (number of days per month) for each formulation were obtained. A life events calendar and a photo book of hormone replacement medications used in the United States were utilized to enhance recall. Our questioning with regard to all of these factors was limited to exposures that occurred before each subject's reference date. The reference date used for each woman with breast cancer was her date of diagnosis. Control reference dates were assigned so as to reflect the expected distribution of reference dates among the cases.

Analysis

In our HRT analyses, the referent category consisted of women who never used any type of HRT or who used HRT for a total of less than 6 months. Excluded from the analysis were women whose only HRT use consisted of 6 months or more of shots, creams, or suppository use (3 controls, 5 cases). Our analysis of ever use of ERT was restricted to women who were exclusive users of ERT, that is women who had never also used CHRT for 6 months or longer. This restriction was made because in prior studies CHRT has been observed to be more strongly associated with breast cancer risk than is ERT.[12,13] As a result of this restriction, 69 controls (15%) and 95 cases (21%) were excluded from our analysis. With regard to patterns of CHRT use, estrogen users who took progestin <25 days per month were considered sequential CHRT (SCHRT) users, and those who used progestin $\geq$25 days per month were considered continuous CHRT (CCHRT) users.

We compared all breast cancer cases to controls using unconditional logistic regression,[14] and then compared ILC and IDC cases to controls using polytomous logistic regression.[15] The 123 women with other breast cancer histologies were excluded from the latter analysis. Both statistical approaches were used to calculate odds ratios (ORs) as an estimate of the relative risk and to compute 95% confidence intervals (CIs). The following variables were evaluated as potential confounders: family history of breast cancer (first degree, no first degree); education (less than high school, high school graduate, some college, college graduate or higher); type of menopause (natural, induced, simple hysterectomy (hysterectomy without a bilateral oophorectomy)); age at menopause (five-year categories); age at menarche (≤11, 12-13, ≥14); parity; age at first full-term (>26 weeks) pregnancy (never pregnant, 14-19, 20-24, 25-29, ≥30 years); body mass index (BMI) five years prior to reference date (quartiles of control population); average daily alcohol use during the twenty years prior to reference date (none, ≤8.1 grams, ≥8.2 grams); and oral contraceptive use (never, <5 years, ≥5 years). Only adjustment for type of menopause changed the risk estimates of the odds ratios of interest by more than 10%. Therefore, all analyses were adjusted for type of menopause and for age (continuous) since cases and controls were matched on age.

RESULTS

Women with breast cancer had a similar age distribution as controls, no matter what the histology of their tumor (Table 1.1). Controls were more likely than cases to be non-white. Both ILC and IDC cases were somewhat more likely than controls to have an earlier age at menarche, to be older at the time of their first birth, to have a first degree family history of breast cancer, and to have higher levels of alcohol consumption. IDC cases were more likely to be never users of oral contraceptives, while ILC cases were more likely to have used oral contraceptives for ≥5 years compared to controls. Otherwise ILC cases, IDC cases, and controls were similar to each other with respect to other demographic and reproductive characteristics.

Among women who never used CHRT, neither ever use of ERT nor long durations of ERT use appeared to alter breast cancer risk (Table 1.2). For example, 12.3% of controls and 10.8% of cases used ERT for ≥25 years (odds ratio (OR) = 0.9; 95% CI: 0.7-1.3). Neither current users nor former users of unopposed estrogen (ERT) for 6 months or longer had an elevated risk of breast cancer, whether for all histologic types combined, IDC, or ILC.

Ever use of CHRT, among women who never used ERT, was associated with a 1.8-fold (95% CI: 1.3-2.4) elevated risk of breast cancer overall, and with increases in risk of both IDC and ILC (OR=1.7; 95% CI: 1.2-2.4 and OR=2.5; 95% CI: 1.5-4.1, respectively) (Table 1.3). These elevations in risk were greatest among women who used CHRT for ≥5 years or longer. Users of CHRT for 5-15 years and ≥15 years had 1.7 and 1.9-fold increases in risk of IDC, respectively, and 3.3 and 2.3-fold increases in risk of ILC, respectively. Similar results were obtained when the analysis included CHRT users who had also ever used ERT. Current and former use of CHRT for 6 months or longer were also associated with increased risks of all histologic types of breast cancer, and of lobular and ductal tumors separately. Specifically, current use of CHRT was associated with 2.0, 1.8, and 3.0-fold elevations in risk of all histologic types, ductal, and lobular breast cancer, respectively.

The elevations in risk associated with ever and current use of CHRT differed little by the pattern of progestin use (Table 1.4). Specifically, ever use of both SCHRT and CCHRT were associated with elevations in risk of breast cancer of all histologic types (OR=1.9; 95% CI: 1.3-2.7 and OR=1.7; 95% CI: 1.3-2.3, respectively) that increased in magnitude as duration of use increased. Similarly, ever use of SCHRT and CCHRT were associated with increased risks of both IDC (OR=1.7; 95% CI: 1.1-2.6 and OR=1.6; 95% CI: 1.1-2.2, respectively) and ILC (OR=2.7; 95% CI: 1.4-5.0 and OR=2.6; 95% CI: 1.6-4.2, respectively).

DISCUSSION

Certain limitations of our study should be considered when interpreting the results. We did not conduct an independent pathology review of the tumors, but instead relied on the

diagnoses made by numerous pathologists in the Seattle-Puget Sound area. Misclassification of tumor histology may have resulted in some instances.

Additionally, we were able to interview only 80.6% of all eligible cases and 73.8% of all eligible controls. Our results could be biased if the women we were unable to interview differed from those who did participate with regard to type or patterns of hormone use. We also relied on participants' recall of the types of HRT used as well as the timing and duration of use. However, studies have shown reasonable agreement between postmenopausal women's reports and physicians' or medical records.[16-19] Also of note is that the majority of women who ever used CHRT in our study were current users (83.3% of cases, 82.1% of controls), likely increasing their ability to accurately report the specific regimens they have used.

Our results suggest that ERT use does not increase risk of breast cancer in women 65-79 years of age, even among users of ERT for ≥25 years. However, the meta-analysis by the Collaborative Group on Hormonal Factors in Breast Cancer found that current use of ERT for ≥5 years was associated with a 1.34-fold increased risk of breast cancer.[1] This meta-analysis was limited though, in that data on the type of HRT used were only available for 39% of the eligible women, and because the analysis was not restricted to women who were exclusive users of ERT. As a result, some of the association that was observed may have been due to a mixing of the effects of ERT use with CHRT use, for this study and others have found that CHRT use is a stronger risk factor for breast cancer than is ERT use.[12,13] In a prior meta-analysis that was based primarily on studies conducted before widespread use of CHRT, use of ERT for ≥10 years was associated with a 15%-49% increased risk of breast cancer.[20] It is noteworthy though that results from the Nurse's Health Study from 1976 to 1986, a time period prior to the widespread use of CHRT, are consistent with our results as we both found that ≥15 years of ERT use was not associated with an increased risk of breast cancer.[21] These results were not included in the meta-analysis by Steinberg, et al. as they included results from the Nurse's Health Study that were published later[22] and included a larger proportion of CHRT users. Also, few studies have focused on older women, and none of the studies described above looked specifically at

durations of ≥25 years of ERT use. Thus, our finding that long-term exclusive use of ERT is not associated with an elevation in breast cancer risk among women 65-79 years of age needs to confirmed by others.

The results of our study are in partial agreement with the five studies that have evaluated associations between HRT use and the occurrence of ILC and IDC.[3-7] With respect to ERT use, our findings are consistent with four of these five studies in finding that ERT does not increase risk of ILC[3,4,6,7] or IDC.[3-5,7] These studies have also observed that CHRT use is associated with a 2.0 to 3.9-fold increased risk of ILC. Similarly, we found that ever use of CHRT is associated with a 2.5-fold elevation in ILC risk. Though each of these studies also observed that CHRT use is more strongly associated with ILC than it is with IDC, similar to only one of the previous five studies[6] we observed that CHRT use is also associated with a 1.6-fold elevated risk of IDC. However, there are also some important differences between our study and these previous reports. Specifically, four of these five studies consisted only of cases diagnosed before 1995, and they all included younger post-menopausal women. Our study focused on older women who were diagnosed in more recent years (1997-1999), resulting in a relatively high prevalence of use of both ERT and CHRT for long durations. This provided us with greater power to measure the relationships between long durations of HRT use and risks of ILC and IDC. Consistent with the hypothesis that CHRT use may have a different effect on the risk of ILC and IDC, lobular carcinomas are more likely to be both estrogen and progesterone receptor positive compared to ductal carcinomas, suggesting that the former are more likely to be hormonally responsive. Additionally, progesterone has long been known to promote lobular differentiation.[23] It is also known that ILCs and IDCs differ with respect to the expression of a variety molecular tumor markers other than hormone receptors, including cyclin D1,[24] VEGF,[25] and e-cadherin.[26]

Two of the five studies also reported on breast cancer risk by different patterns of CHRT use. One found that both SCHRT and CCHRT use were associated with an increased risk of ILC and with an increased risk of IDC that was within the limits of chance,[5] while the other observed that only CCHRT was associated with an increased risk of ILC.[7] Similar to the former study, our

results suggest that use of both SCHRT and CCHRT increase ILC risk, and (to a lesser extent) IDC risk. One limitation of the WHI is that it only evaluated CCHRT use, and thus conclusions regarding the effect of SCHRT or other CHRT regimens on breast cancer risk could not be drawn. However, our data and the data from Chen, et al.[5] suggest that SCHRT and CCHRT are equivalent with respect to the risks of breast cancer associated with their use.

Evidence is mounting regarding the adverse effects of adding progestin to HRT in regards to breast cancer risk. The primary strength of our study is that it included women with long durations of CHRT use, and it provides additional evidence that both short-term and long-term CHRT use, whether taken in a sequential or continuous manner, are associated with elevations in risks of ILC and IDC. However, while risk of IDC was highest among women who used CHRT for ≥15 years or longer, users of CHRT for 5-15 years actually had a higher risk of ILC than did users for ≥15 years. We were limited though in our number of ILC cases and there was considerable overlap in the 95% confidence intervals of these latter two estimates. Thus, larger studies are needed to evaluate the dose-response relationship between CHRT use and ILC risk. Clearly though, the risk of breast cancer associated with CHRT use does appear to vary by histologic type. Given the known heterogeneity of breast cancer, differences in etiologic associations are not unexpected. Thus, a greater understanding of the etiology and risk factors of different histologic types of breast cancer may aid in the development of improved management and treatment approaches to women with breast cancer.

Table 1.1: Distribution of demographic and known risk factors for breast cancer among 1,007 controls, 975 breast cancer cases, 656 ductal cases, and 196 lobular cases

	Controls (n=1,007)		All cases (n=975)		Ductal (n=656)		Lobular (n=196)	
Characteristic	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Reference age								
65-69	330	32.8	300	30.8	204	31.1	58	29.6
70-74	381	37.8	381	39.1	252	38.4	85	43.4
75-79	296	29.4	294	30.2	200	30.5	53	27.0
Race								
White	925	91.9	929	95.3	623	95.0	188	95.9
Black	37	3.7	16	1.6	11	1.7	3	1.5
Asian/Pacific Islander	29	2.9	19	1.9	18	2.7	1	0.5
Other/unknown	16	1.6	11	1.1	4	0.6	4	2.0
Income								
<$15,000	191	21.7	177	21.3	124	22.1	30	17.9
$15,000-$25,000	214	24.3	198	23.9	139	24.8	39	23.2
$25,000-$50,000	296	33.6	296	35.7	204	36.4	60	35.7
≥$50,000	180	20.4	159	19.2	94	16.8	39	23.2
Missing	126		145		95		28	
Marital status								
Married	536	54.6	517	54.4	343	53.8	103	53.4
Widowed	315	32.1	301	31.7	201	31.6	65	33.7
Divorced/separated	121	12.3	125	13.1	87	13.7	23	11.9
Single	10	1.0	8	0.8	6	0.9	2	1.0
Missing	25		24		19		3	
Education								
Less than high school	153	15.2	126	12.9	87	13.3	19	9.7
High school graduate	395	39.3	376	38.6	251	38.3	84	42.9
Some college	286	28.4	312	32.0	210	32.0	59	30.1
College graduate	172	17.1	161	16.5	108	16.5	34	17.3
Missing	1		0		0		0	
Age at menarche								
8-11	173	17.2	182	18.8	126	19.4	35	17.9
12-13	520	51.7	525	54.2	357	54.8	104	53.1
≥14	313	31.1	261	27.0	168	25.8	57	29.1
Missing	1		7		5		0	
Parity								
Nulliparous	94	9.3	88	9.0	57	8.7	20	10.2
Parous	913	90.7	887	91.0	599	91.3	176	89.8

Table 1.1, continued

Age at first birth	187	20.5	152	17.2	98	16.4	31	17.6
14-19	435	47.7	432	48.9	302	50.7	84	47.7
20-24	205	22.5	206	23.3	136	22.8	41	23.3
25-29	85	9.3	93	10.5	60	10.1	20	11.4
≥30	95		92		60		20	
Missing	187	20.5	152	17.2	98	16.4	31	17.6
Type of menopause								
Natural	607	61.6	583	61.4	400	62.8	113	59.8
Induced	148	15.0	129	13.6	78	12.2	29	15.3
Simple hysterectomy	231	21.6	237	25.0	159	25.0	47	24.9
Missing	21		26		19		7	
Age at menopause								
23-39	64	9.9	38	6.6	29	7.6	4	3.6
40-44	99	15.3	77	13.4	40	10.5	19	17.0
45-49	172	26.6	165	28.7	116	30.4	27	24.1
50-54	222	34.3	217	37.8	143	37.4	47	42.0
55-68	90	13.9	77	13.4	54	14.1	15	13.4
Missing	360		401		274		84	
Duration of oral contraceptive use								
never	752	75.4	736	76.0	508	78.0	141	72.3
<5 years	159	15.9	139	14.4	85	13.1	30	15.4
≥5 years	86	8.6	93	9.6	58	8.9	24	12.3
Missing	10		7		5		1	
First degree family history of breast cancer								
No	771	82.9	703	77.2	469	77.1	146	78.5
Yes	159	17.1	208	22.8	139	22.9	40	21.5
Missing	77		64		48		10	
Body mass index, quartiles								
≤23.32	261	27.1	209	22.3	139	22.0	51	27.1
23.33-26.20	241	25.0	240	25.6	164	25.9	43	22.9
26.21-30.11	230	23.9	245	26.1	162	25.6	52	27.7
≥30.12	231	24.0	245	26.1	168	26.5	42	22.3
Missing	44		36		23		8	
Average number of grams of alcohol per day								
None	518	51.6	461	47.5	320	49.1	78	39.8
<8.2	248	24.7	249	25.7	158	24.2	61	31.1
≥8.2	238	23.7	260	26.8	174	26.7	57	29.1
Missing	3		5		4		0	

Table 1.2: Use of unopposed estrogen replacement therapy (ERT) and risk of overall and specific histologic types of breast cancer

	Controls N = 1,007		Overall N = 975				Ductal N = 656				Lobular N = 196			
Regimen	**N**	**%**	**N**	**%**	**OR***	**95% CI**	**N**	**%**	**OR**	**95% CI**	**N**	**%**	**OR**	**95% CI**
Exclusive ERT use†														
Never	413	41.0	352	36.1	**1.0**	(ref)	243	37.0	**1.0**	(ref)	59	30.1	**1.0**	(ref)
Ever	397	39.4	360	36.9	**1.0**	(0.8-1.3)	240	36.6	**1.0**	(0.8-1.3)	75	38.3	**1.2**	(0.8-1.9)
6 months-5 years	113	11.2	79	8.1	**0.8**	(0.6-1.1)	56	8.5	**0.8**	(0.6-1.2)	17	8.7	**1.1**	(0.6-1.9)
5-15 years	83	8.2	90	9.2	**1.2**	(0.8-1.7)	60	9.1	**1.2**	(0.8-1.7)	19	9.7	**1.5**	(0.8-2.8)
15-25 years	77	7.6	86	8.8	**1.3**	(0.9-1.9)	61	9.3	**1.4**	(0.9-2.1)	14	7.1	**1.3**	(0.7-2.6)
≥25 years	124	12.3	105	10.8	**0.9**	(0.7-1.3)	63	9.6	**0.8**	(0.6-1.2)	25	12.8	**1.3**	(0.7-2.3)
Recency of ERT use among exclusive ERT users§														
Never	413	41.0	352	36.1	**1.0**	(ref)	243	37.0	**1.0**	(ref)	59	30.1	**1.0**	(ref)
Former	123	12.2	119	12.2	**1.0**	(0.8-1.4)	83	12.7	**1.1**	(0.8-1.5)	22	11.2	**1.2**	(0.7-2.1)
Current	274	27.2	241	24.7	**1.0**	(0.8-1.3)	157	23.9	**1.0**	(0.7-1.3)	53	27.0	**1.3**	(0.8-2.1)
6 months-5 years	42	4.2	18	1.8	**0.5**	(0.3-0.9)‡	12	1.8	**0.5**	(0.3-1.0)‡	6	3.1	**1.1**	(0.4-2.8)
5-15 years	49	4.9	50	5.1	**1.2**	(0.8-1.9)	34	5.2	**1.2**	(0.7-2.0)	11	5.6	**1.8**	(0.8-3.8)
≥15 years	183	18.2	173	17.7	**1.1**	(0.8-1.5)	111	16.9	**1.1**	(0.8-1.5)	36	18.4	**1.4**	(0.8-2.5)

* All models are adjusted for reference age and type of menopause.

† Never users defined as never users of HRT or users of any type of HRT for <6 months; ever users defined as users of ERT for ≥6 months who never used CHRT for ≥6 months.

‡ $p < 0.05$.

§ Never users defined as never users of HRT or users of any type of HRT for <6 months; former users defined as former users of ERT for ≥6 months; current users defined as users of ERT for ≥6 months with last use within the 6 months prior to reference date. All former and current ERT users never used CHRT for ≥6 months.

Table 1.3: Use of combined estrogen and progestin hormone replacement therapy (CHRT) and risk of overall and specific histologic types of breast cancer

	Controls N = 1,007		Overall N = 975				Ductal N = 656				Lobular N = 196			
Regimen	**N**	**%**	**N**	**%**	**OR***	**95% CI**	**N**	**%**	**OR**	**95% CI**	**N**	**%**	**OR**	**95% CI**
Exclusive ever use of CHRT†														
Never	413	41.0	352	36.1	**1.0**	(ref)	243	37.0	**1.0**	(ref)	59	30.1	**1.0**	(ref)
Ever	96	9.5	137	14.1	**1.8**	(1.4-2.5)‡	89	13.6	**1.7**	(1.2-2.4)‡	19	9.7	**2.5**	(1.5-4.1)‡
6 months-5 years	29	2.9	30	3.1	**1.4**	(0.8-2.3)	23	3.5	**1.5**	(0.8-2.6)	5	2.6	**1.4**	(0.5-3.7)
5-15 years	37	3.7	57	5.8	**2.1**	(1.3-3.3)‡	33	5.0	**1.7**	(1.0-2.9)‡	15	7.7	**3.3**	(1.6-6.5)‡
≥15 years	30	3.0	50	5.1	**2.1**	(1.3-3.3)‡	33	5.0	**1.9**	(1.1-3.2)‡	9	4.6	**2.3**	(1.0-5.1)‡
Ever use of CHRT†														
Never	413	41.0	352	36.1	**1.0**	(ref)	243	37.0	**1.0**	(ref)	59	30.1	**1.0**	(ref)
Ever	165	16.4	232	23.8	**1.7**	(1.3-2.2)‡	148	22.6	**1.6**	(1.2-2.1)‡	58	29.6	**2.6**	(1.7-4.0)‡
6 months-5 years	60	6.0	65	6.7	**1.4**	(0.9-2.0)	46	7.0	**1.4**	(0.9-2.1)	14	7.1	**1.8**	(1.0-3.5)
5-15 years	63	6.3	101	10.4	**2.0**	(1.4-2.9)‡	58	8.8	**1.6**	(1.1-2.5)‡	30	15.3	**3.6**	(2.0-6.2)‡
≥15 years	42	4.2	66	6.8	**1.8**	(1.2-2.8)‡	44	6.7	**1.7**	(1.1-2.7)‡	14	7.1	**2.5**	(1.3-4.9)‡

* All models are adjusted for reference age and type of menopause.

† Never users defined as never users of HRT or users of any type of HRT for <6 months; ever users defined as users of CHRT for ≥6 months with exclusive CHRT users including only those who ever used CHRT but never used ERT for ≥6 months.

‡ $p < 0.05$.

Table 1.3, continued

Regimen	Controls N = 1,007 N	%	Overall N = 975 N	%	OR*	95% CI	Ductal N = 656 N	%	OR	95% CI	Lobular N = 196 N	%	OR	95% CI
Recency of CHRT use[§]														
Never	413	41.0	352	36.1	**1.0**	(ref)	243	37.0	**1.0**	(ref)	59	30.1	**1.0**	(ref)
Former	20	2.0	32	3.3	**2.0**	(1.1-3.7)‡	23	3.5	**2.1**	(1.1-3.9)‡	5	2.6	**1.9**	(0.7-5.4)
Current	115	11.4	178	18.3	**2.0**	(1.5-2.7)‡	113	17.2	**1.8**	(1.3-2.5)‡	44	22.4	**3.0**	(1.9-4.9)‡
6 months-5 years	32	3.2	31	3.2	**1.3**	(0.8-2.2)	24	3.7	**1.4**	(0.8-2.5)	5	2.6	**1.3**	(0.5-3.5)
5-15 years	50	5.0	87	8.9	**2.3**	(1.5-3.4)‡	49	7.5	**1.8**	(1.2-2.9)‡	27	13.8	**4.4**	(2.5-7.8)‡
≥15 years	33	3.3	60	6.2	**2.2**	(1.4-3.5)‡	40	6.1	**2.1**	(1.3-3.4)‡	12	6.1	**2.8**	(1.3-5.8)‡

§ Never users defined as never users of HRT or users of any HRT for <6 months; former users defined as former users of CHRT for ≥6 months who are not current ERT users; current users defined as users of CHRT for ≥6 months with last use within the 6 months prior to reference date.

Table 1.4: Relationship of ever use of different regimens of combined estrogen and progestin hormone replacement therapy to risk of overall and specific histologic types of breast cancer by duration

	Controls N = 1,007		Overall N = 975				Ductal N = 656				Lobular N = 196			
Regimen	**N**	**%**	**N**	**%**	**OR***	**95% CI**	**N**	**%**	**OR**	**95% CI**	**N**	**%**	**OR**	**95% CI**
Sequential (use of progestin for <25 days per month) therapy (SCHRT)														
Ever use of SCHRT†														
Never	413	41.0	352	36.1	**1.0**	(ref)	243	37.0	**1.0**	(ref)	59	30.1	**1.0**	(ref)
Ever	55	5.5	80	8.2	**1.9**	(1.3-2.7)‡	52	7.9	**1.7**	(1.1-2.6)‡	19	9.7	**2.7**	(1.4-5.0)‡
6 months-5 years	22	2.2	26	2.7	**1.6**	(0.9-2.9)	17	2.6	**1.5**	(0.8-2.9)	6	3.1	**2.2**	(0.8-5.8)
5-15 years	24	2.4	33	3.4	**1.7**	(1.0-3.1)	21	3.2	**1.6**	(0.8-3.0)	8	4.1	**2.4**	(1.0-6.0)
≥15 years	9	0.9	21	2.2	**2.8**	(1.2-6.4)‡	14	2.1	**2.5**	(1.0-6.1)‡	5	2.6	**4.3**	(1.4-13.5)
Current use of SCHRT§														
Never	413	41.0	352	36.1	**1.0**	(ref)	243	37.0	**1.0**	(ref)	59	30.1	**1.0**	(ref)
Former	35	3.5	50	5.1	**1.7**	(1.1-2.8)‡	32	4.9	**1.5**	(0.9-2.6)	13	6.6	**2.8**	(1.3-5.7)‡
Current	20	2.0	30	3.1	**2.1**	(1.1-3.8)‡	20	3.0	**2.0**	(1.0-3.9)‡	6	3.1	**2.5**	(0.9-6.6)
6 months-5 years	4	0.4	3	0.3	**1.3**	(0.3-6.4)	2	0.3	**1.2**	(0.2-7.4)	1	0.5	**2.5**	(0.3-25.0)
≥5 years	16	1.6	27	2.8	**2.3**	(1.2-4.3)‡	18	2.7	**2.2**	(1.1-4.4)‡	5	2.6	**2.5**	(0.8-7.1)

Table 1.4, continued

Regimen	Controls N = 1,007 N	%	Overall N = 975 N	%	OR*	95% CI	Ductal N = 656 N	%	OR	95% CI	Lobular N = 196 N	%	OR	95% CI
Continuous (use of progestin for ≥25 days per month) therapy (CCHRT)														
Ever use of CCHRT†														
Never	413	41.0	352	36.1	**1.0**	(ref)	243	37.0	**1.0**	(ref)	59	30.1	**1.0**	(ref)
Ever	116	11.5	159	16.3	**1.7**	(1.3-2.3)‡	102	15.5	**1.6**	(1.1-2.2)‡	40	20.4	**2.6**	(1.6-4.2)‡
6 months-5 years	52	5.2	57	5.8	**1.4**	(0.9-2.1)	41	6.3	**1.4**	(0.9-2.2)	13	6.6	**1.9**	(1.0-3.8)
5-15 years	43	4.3	69	7.1	**2.1**	(1.4-3.1)‡	40	6.1	**1.7**	(1.1-2.7)‡	19	9.7	**3.4**	(1.8-6.4)‡
≥15 years	21	2.1	33	3.4	**1.9**	(1.0-3.3)‡	21	3.2	**1.7**	(0.9-3.1)	8	4.1	**2.8**	(1.2-6.6)‡
Current use of CCHRT§														
Never	413	41.0	352	36.1	**1.0**	(ref)	243	37.0	**1.0**	(ref)	59	30.1	**1.0**	(ref)
Former	26	2.6	22	2.3	**1.1**	(0.6-1.9)	15	2.3	**1.0**	(0.5-2.0)	5	2.6	**1.5**	(0.5-4.0)
Current	90	8.9	137	14.1	**1.9**	(1.4-2.6)‡	87	13.3	**1.7**	(1.2-2.5)‡	35	17.9	**3.0**	(1.8-5.0)‡
6 months-5 years	35	3.5	41	4.2	**1.5**	(0.9-2.4)	31	4.7	**1.6**	(1.0-2.7)	8	4.1	**1.8**	(0.8-4.1)
≥5 years	55	5.5	96	9.8	**2.2**	(1.5-3.3)‡	56	8.5	**1.9**	(1.2-2.8)‡	27	13.8	**3.8**	(2.2-6.7)‡

* All models are adjusted for reference age and type of menopause.

† Never users defined as never users of any type of HRT or users of any type of HRT for less than 6 months; former users defined as former users of SCHRT (or CCHRT) for 6 months or longer who are not current ERT users; current users defined as users of SCHRT (or CCHRT) for ≥6 months with last use within the 6 months prior to reference date.

‡ $p < 0.05$.

§ Never users defined as never users of HRT or users of any type of HRT for <6 months; ever users defined as users for ≥6 months.

NOTES TO CHAPTER 1

1. Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and hormone replacement therapy: collaborative reanalysis of data from 51 epidemiological studies of 52,705 women with breast cancer and 108,411 women without breast cancer. Lancet 1997;350:1047-1059.
2. Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. JAMA 2002;288:321-333.
3. Newcomer LM, Newcomb PA, Daling JR, Yasui Y, Potter JD. Post-menopausal hormone use and risk of breast cancer by histologic type. Am J Epidemiol 1999;149:S79.
4. Li CL, Weiss NS, Stanford JL, Daling JR. Hormone replacement therapy in relation to risk of lobular and ductal breast carcinoma in middle-aged women. Cancer 2000;88:2570-2577.
5. Chen CL, Weiss NS, Newcomb P, Barlow W, White E. Hormone replacement therapy in relation to breast cancer. JAMA 2002;287:734-741.
6. Newcomb PA, Titus-Ernstoff L, Egan KM, et al. Postmenopausal estrogen and progestin use in relation to breast cancer risk. Cancer Epidemiol Biomarker Prev 2002;11:593-600.
7. Daling JR, Malone KE, Doody DR, et al. Relation of Regimens of Combined Hormone Replacement Therapy to Lobular, Ductal, and Other Histologic Types of Breast Carcinoma. Cancer 2002;in press.
8. Stierer M, Rosen H, Weber R, Hanak H, Spona J, Tuchler H. Immunohistochemical and biochemical measurement of estrogen and progesterone receptors in primary breast cancer: Correlation of histopathology and prognostic factors. Ann Surg 1993;218:13-21.
9. Du Toit RS, Locker AP, Ellis IO, et al. An evaluation of differences in prognosis, recurrence patterns and receptor status between invasive lobular and other invasive carcinomas of the breast. Eur J Surg Oncology 1991;17:251-257.
10. Dixon J, Anderson T, Page D, Lee D, Duffy S. Infiltrating lobular carcinoma of the breast. Histopathology 1982;6:149-161.

11. Li CL, Anderson BO, Porter P, Holt SK, Daling JR, Moe RE. Changing incidence rate of invasive lobular breast carcinoma among older women. Cancer 2000;88:2561-2569.

12. Colditz GA, Hankinson SE, Hunter DJ, et al. The use of estrogens and progestins and the risk of breast cancer in postmenopausal women. New Engl J Med 1995;332:1589-1593.

13. Ross RK, Paganini-Hill A, Wan PC, Pike MC. Effect of hormone replacement therapy on breast cancer risk: estrogen versus estrogen plus progestin. J Natl Cancer Inst 2000;92:328-332.

14. Breslow NE, Day NE. The Analysis of Case-Control Studies. Lyon, France: International Agency for Research on Cancer; 1980.

15. Begg CB, Gray R. Calculation of polychotomous logistic regression parameters using individualized regressions. Biometrika 1984;71:11-18.

16. Pagnini-Hill A, Ross RK. Reliability of recall of drug usage and other health-related information. Am J Epidemiol 1982;116:114-122.

17. Goodman MT, Nomura AMY, Wilkins LR, Kolonel LN. Agreement between interview information and physician records on history of menopausal estrogen use. Am J Epidemiol 1990;131:815-825.

18. Persson I, Bergkvist L, Adami H-O. Reliability of women's histories of climacteric oestrogen treatment assessed by prescription forms. Int J Epidemiol 1987;16:222-228.

19. Jain MG, Rohan TE, Howe GR. Agreement of self-reported use of menopausal hormone replacement therapy with physician reports. Epidemiology 1999;10:260-263.

20. Steinberg KK, Smith SJ, Thacker SB, Stroup DF. Breast cancer risk and duration of estrogen use: the role of study design in meta-analysis. Epidemiology 1994;5:415-421.

21. Colditz GA, Stampfer MJ, Willett WC, Hennekens CH, Rosner B, Speizer FE. Prospective study of estrogen replacement therapy and risk of breast cancer in postmenopausal women. JAMA 1990;264:2648-2653.

22. Colditz GA, Stampfer MJ, Willett WC, et al. Type of postmenopausal hormone use and risk of breast cancer: 12-year follow-up from the Nurses' Health Study. Cancer Causes Control 1992;3:433-439.

23. Azzopardi GJ. Problems in Breast Pathology (1st ed). Eastbourne: WB Saunders, 1979; Chapter 11: 240-257.

24. Oyama T, Kashiwabara K, Yoshimoto K, Arnold A, Koerner F. Frequent overexpression of the cyclin D1 oncogene in invasive lobular carcinoma of the breast. Cancer Res 1998;58:2876-2880.

25. Lee AH, Dublin EA, Bobrow LG, Poulsom R. Invasive lobular and invasive ductal carcinoma of the breast show distinct patterns of vascular endothelial growth factor expression and angiogenesis. J Pathol 1998;185:394-401.

26. Acs G, Lawton TJ, Rebbeck TR, LiVolsi VA, Zhang PJ. Differential expression of E-cadherin in lobular and ductal neoplasms of the breast and its biologic and diagnostic implications. Am J Clin Pathol 2001;115:85-98.

CHAPTER 2:

Reproductive and Anthropometric Factors in Relation to the Risk of Lobular and Ductal Breast Carcinoma among Women 65-79 Years of Age

ABSTRACT

Background: Recent studies report that use of combined estrogen and progestin hormone replacement therapy increases a woman's risk of invasive lobular breast carcinomas (ILC), but has a more modest impact on her risk of invasive ductal carcinomas (IDC). These data suggest that ILCs are more hormonally responsive and may be more strongly associated with hormonally related breast cancer risk factors such as reproductive and anthropometric characteristics. However, few studies have evaluated these risk factors by breast cancer histology.

Methods: A population-based case-control study of women 65-79 years of age was conducted in western Washington State. The responses of 975 women diagnosed with invasive breast cancer during 1997-1999 were compared to those of 1,007 controls. Associations between various reproductive and anthropometric factors and risks of IDC (n=656) and ILC (n=196) were evaluated using polytomous logistic regression.

Results: Earlier age at menarche, later age at menopause, and obesity were more strongly associated with an increased risk of IDC than ILC. Alternatively, though within the limits of chance, five or more years of oral contraceptive use increased risk of ILC but not IDC.

Conclusions: Associations between certain reproductive and anthropometric factors and breast cancer risk differed by histologic type. Additional studies are needed to confirm our results that suggest that factors influencing endogenous hormone levels and duration of ovarian function are more strongly associated with risk of IDC than with risk of ILC, while exogenous hormones are more strongly associated with ILC risk than with IDC risk.

INTRODUCTION

Five recent studies have reported that combined estrogen and progestin hormone replacement therapy (CHRT) use is associated with a 2.0 to 3.9-fold increased risk of invasive lobular carcinoma (ILC), the second most common histologic type of breast cancer, but has a more modest association with the most common histologic type, invasive ductal carcinoma (IDC).[1-5] ILCs are also more likely to be estrogen and progesterone receptor positive compared to IDCs.[6] Thus, the development of lobular breast tumors appears to be under greater hormonal control than is the development of ductal tumors.

There have been numerous investigations of the incidence of breast cancer in relation to factors hypothesized to be involved in hormonal breast carcinogenesis, including a woman's reproductive history and anthropometric characteristics. However, only one study has evaluated the relationship between reproductive factors and the incidence of ILC.[7] That study compared 321 women with lobular and tubular breast cancer to 2,407 women with other histologic types of breast cancer. It found that women with lobular and tubular carcinomas were more likely to be older at the time of their first live birth and to have ever used oral contraceptives, but that age at menarche and number of first live births did not differ by histology. However, this study did not include a control group of women without breast cancer, and 82% of its subjects were pre-menopausal at the time of their breast cancer diagnosis. Since ILC incidence rates are rising only among postmenopausal women[8] and risk factors for breast cancer vary by age and menopausal status,[9] studies evaluating whether or not known hormonal risk factors for breast cancer have different associations with risk of ILC compared to IDC among postmenopausal women are warranted.

Using data from a population-based case-control study of breast cancer, we evaluated the influence that reproductive and anthropometric factors have on risk of ILC and IDC among women 65 to 79 years of age.

METHODS

We conducted a population-based case-control study of women 65-79 years of age living in the three county Seattle-Puget Sound metropolitan area. Study interviewers conducted in-person interviews on all subjects.

Cases

Women aged 65-79 years with no previous history of *in-situ* or invasive breast cancer who were diagnosed with invasive breast cancer between April 1, 1997 and May 31, 1999, were eligible as cases. The Cancer Surveillance System (CSS), the population-based tumor registry that serves the Seattle-Puget Sound region of Washington State and participates in the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute, was used to identify cases. In order to be eligible for the study, cases had to live in King, Pierce, or Snohomish counties and have a Health Care Financing Administration (HCFA) record, since these records were used to identify controls. Of the 1,210 eligible cases identified, 975 (80.6%) were interviewed. Information on tumor histology was ascertained from CSS, which abstracts data on tumor characteristics from medical records and pathology reports from institutions serving the area. CSS classifies histology using the International Classification of Diseases for Oncology (ICD-O) codes. We divided cases into two groups, with codes 8520 and 8522 used to define the 196 ILC cases and code 8500 used to define the 656 IDC cases.

Controls

HCFA records were used to identify women from the general population of female residents of King, Pierce, and Snohomish counties who were the same ages as cases to serve as controls. Of the 1,365 eligible women selected as controls, 1,007 (73.8%) were interviewed.

Data Collection

Informed consent was obtained from all study subjects. Both cases and controls were interviewed in-person and were asked about menstrual, contraceptive and reproductive histories, body size, use of hormone replacement therapy (HRT), and medical history, including family history of cancer. Our questioning with regard to all of these factors was limited to exposures that

occurred before each subject's reference date. The reference date used for each woman with breast cancer was her date of diagnosis. Control reference dates were assigned so as to reflect the expected distribution of reference dates among the cases. A life events calendar was used to aid subjects' recall of important dates in their reproductive history and of any episodes of oral contraceptive use. Subjects were asked what their weight was one month prior to their reference date and what their maximum lifetime height was. These two measurements were used to calculate body mass index. Demographic data and information on smoking status and alcohol use were also collected.

Analysis

We compared the reproductive and anthropometric characteristics of all breast cancer cases to controls using unconditional logistic regression,[10] and compared ILC and IDC cases to controls using polytomous logistic regression.[11] The 123 women with other breast cancer histologies were excluded from the latter analysis. Both statistical approaches were used to calculate odds ratios (ORs) as an estimate of the relative risk and to compute 95% confidence intervals (CIs). With respect to type of menopause, natural menopause was defined as the spontaneous cessation of menstrual periods or receipt of a simple hysterectomy after age 55, and induced menopause was defined as having a hysterectomy with a bilateral oophorectomy or having menstrual periods cease as a result of treatment with chemotherapy prior to reference date. Women who could not be classified into either of these categories, including those who had a hysterectomy without a bilateral oophorectomy before age 55, were considered to have an unknown type of menopause. Age at menopause was classified as age when natural or induced menopause occurred, but was unknown for women with an unknown type of menopause.

The following variables were evaluated as potential confounders for each reproductive and anthropometric factor we assessed: race (white, black, Asian/Pacific Islander, other/unknown), income (<$15,000, $15-$25,000, $25-50,000, >$50,000), marital status (married, widowed, divorced/separated, single never married), education (less than high school, high school graduate, some college, college graduate or higher), family history of breast cancer (first

degree, no first degree), average weekly alcohol use during the twenty years prior to reference date (none, <7 drinks, ≥7 drinks), duration of unopposed estrogen HRT use (never or <6 months, 6 months to 5 years, 5 or more years), and duration of CHRT use (never or <6 months, 6 months to 5 years, 5 or more years). We adjusted all analyses for age (continuous) since cases and controls were matched on age. We also adjusted analyses of breast cancer incidence in relation to: type of menopause for duration of CHRT use; age at menopause for first degree family history of breast cancer; and height and BMI for income, because adjustment for each of these additional factors changed the risk estimates by more than 10%.

RESULTS

Both lobular and ductal cases had a similar age distribution as controls (Table 2.1). Controls were more likely than cases to be non-white, and IDC cases were more likely than ILC cases to be Asians/Pacific Islanders. Controls were somewhat more likely to have less than a high school education than cases. Both ILC and IDC cases were also more likely than controls to have a first-degree family history of breast cancer and to have higher levels of alcohol consumption. ILC cases were more likely than both IDC cases and controls to have used unopposed estrogen HRT and CHRT for 5 years or longer. Otherwise ILC cases, IDC cases, and controls were similar to each other with respect to the other demographic characteristics we assessed.

With respect to reproductive factors, women with a late age at menarche had a 20% decrease in their overall risk of breast cancer though this finding was within the limits of chance (Table 2.2). There was a suggestion that this risk varied by histologic type as compared to women with an age at menarche at age 8 to 11, women with an age at menarche at age 14 years and older had a 30% (95% CI: 0.5-1.0) decreased risk of IDC, but only a 10% (95% CI: 0.6-1.4) decreased risk of ILC. Though parity did not alter breast cancer risk, compared to women who had only one full term birth, women who had four or more full term births had decreased risks of both IDC and ILC. Compared to women who were 19 years of age or younger at the time of their

first full term birth, women who were older when they had their first full term birth had increased risks of all histologic types of breast cancer, IDC, and ILC, though these increases were within the limits of chance. Though also within the limits of chance, users of oral contraceptives for 5 years or longer had a 1.6-fold increased risk of ILC (95% CI: 1.0-2.6), but did not have an increased risk of IDC. Finally, compared to women who experienced menopause at age 44 years or younger, women who were older when they experienced menopause had increased risks of all histologic types of breast cancer, though this increase was primarily limited to women with IDC. For example, compared to women with an age at menopause at age 44 years or younger, women with an age at menopause at age 55 years or older had a 1.8-fold increased risk of IDC (95% CI: 1.1-2.7), but essentially no change in their risk of ILC (OR = 1.2; 95% CI: 0.6-2.4).

With regard to anthropometric factors, compared to women with a height of less than 160 cm, women 160 cm and taller had increased risks of all histologic types of breast cancer, IDC, and ILC, with the highest risks observed for ILC (Table 2.3). Reference weight also altered breast cancer risk as women weighing greater than 130 pounds had 30% to 50% greater risks of breast cancer of all histologic types. Weights greater than 130 pounds were also associated with increases in risk of IDC and ILC, thought the increases in ILC risk were within the limits of chance. Weight at age 30 had little impact on risk of breast cancer, but higher maximum lifetime weights were associated with increases in risk of breast cancer of all histologic types, though this increase was primarily confined to IDC. Compared to women in the lowest quartile of BMI, women in the upper two quartiles had a 40% increase in their risk of breast cancer of all histologic types, though again this increase was primarily limited to IDC. For example, compared to women in the lowest quartile of BMI, women in the highest quartile had a 1.4-fold increased risk of IDC (95% CI: 1.0-1.9), but no change in their risk of ILC (OR = 1.0; 95% CI: 0.6-1.6).

DISCUSSION

Certain limitations of our study should be considered when interpreting the results. We did not conduct an independent pathology review of the tumors, instead we relied on the

diagnoses made by numerous pathologists in the Seattle-Puget Sound area. Misclassification of tumor histology may have resulted in some instances. We were also limited somewhat by a relatively small number of lobular cases.

Additionally, we were only able to interview 80.6% of all eligible cases and 73.8% of all eligible controls. Our results could be biased if the women we were unable to interview differed from those who did participate with regard to their reproductive or anthropometric characteristics. Also, all of our data were based on self-reports. This may have been a particular problem for our analyses of weight and BMI (calculated from self-reported heights and weights) since participants in research studies may underestimate their weight. This issue was addressed in a previous breast cancer case-control study conducted in our area in which participants were weighed and measured at the time of their interview. The correlation between self-reported weight one year before diagnosis and weight measured at the interview for women in this study was $R = 0.89$,[12] suggesting that self-reported weight is a relatively valid measure among women in our population. Finally, the results of our study only apply to women 65-79 years of age, as risk factors for breast cancer can vary by a woman's age and menopausal status.[9]

There is a growing body of evidence that CHRT use is associated with a greater increase in risk of ILC compared to IDC. Consistent with this evidence, ILCs are more likely to be both estrogen and progesterone receptor positive compared to IDCs, suggesting that they are more hormonally responsive. In addition, progesterone has long been known to promote lobular differentiation.[13] However, only one study has evaluated the relationship between reproductive risk factors for breast cancer and risk of ILC. Numerous studies have shown that early age at menarche, late age at menopause, nulliparity, late age at first full-term pregnancy, and low parity are associated with an increased risk of breast cancer as a whole.[9] Additionally, women who are obese and/or tall are at increased risk of postmenopausal breast cancer. The mechanisms underlying these associations are thought to be largely hormonal and related to the influence endogenous estrogen and progesterone have on the breast.[9]

In this study we observed all of these same associations with the exception that we did not observe nulliparity to be a risk factor for breast cancer. The reason for not finding an association with nulliparity is unclear. However, few studies have focused specifically on older women, and nulliparity may not be as an important a risk factor for women 65-79 years of age as it is for younger women.

When we stratified our results by histologic type a few differences were observed. Age at menarche and age at menopause were more strongly associated with risk of IDC than with risk of ILC. These findings suggest that duration of ovarian function may be a stronger risk factor for IDC than it is for ILC. With respect to anthropometric factors, the primary difference between IDC and ILC was related to BMI as obese women had increased risks of IDC but not ILC. Alternatively, we found that while users of oral contraceptives for five years or longer did not have an increased risk of breast cancer of all histologic types or of IDC, they did have an increased risk of ILC. The former result is consistent with the meta-analysis from the Collaborative Group on Hormonal Factors in Breast Cancer, which reported that oral contraceptive use is not a risk factor for postmenopausal breast cancer.[14] Our finding though that oral contraceptive use for 5 years of longer increases risk of ILC is consistent with the report by Stalsberg, et al.[7]

Taken as a whole our results suggest that certain factors that influence endogenous hormone levels are associated with elevations in risks of IDC and ILC of similar magnitudes, while age at menarche, age at menopause, and BMI are associated with IDC risk but not with ILC risk. Taking into account recent data on HRT use, IDC risk appears to be more strongly related to factors that increase endogenous hormone levels or are related to longer durations of ovarian function compared to ILC, while ILC risk is more strongly related to exogenous hormone exposures, both oral contraceptives and CHRT, than is IDC. Additional studies are needed to confirm these results as this is the first population based case-control study to report on how many of these hormonal factors differentially influence risk of ILC and IDC. Though the specific mechanisms underlying these epidemiologic differences are unclear, our results do suggest that pathways leading to ILC and IDC are different. There is a growing body of literature to support

this conclusion as ILCs and IDCs are known to differ with respect to their expression of a variety of molecular tumor markers in addition to estrogen and progesterone receptor, including cyclin D1,[15] VEGF,[16] and e-cadherin.[17] Evaluating how hormonal risk factors influence risk of ILC compared to IDC is important to expand our understanding of the etiology of different histologic types of breast cancer.

Table 2.1: Distribution of demographic and known risk factors for breast cancer among 1,007 controls, 975 breast cancer cases, 656 ductal cases, and 196 lobular cases

	Controls (n=1,007)		All cases (n=975)		Ductal (n=656)		Lobular (n=196)	
Characteristic	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Reference age								
65-69	330	32.8	300	30.8	204	31.1	58	29.6
70-74	381	37.8	381	39.1	252	38.4	85	43.4
75-79	296	29.4	294	30.2	200	30.5	53	27.0
Race								
White	925	91.9	929	95.3	623	95.0	188	95.9
Black	37	3.7	16	1.6	11	1.7	3	1.5
Asian/Pacific Islander	29	2.9	19	1.9	18	2.7	1	0.5
Other/unknown	16	1.6	11	1.1	4	0.6	4	2.0
Income								
<$15,000	191	21.7	177	21.3	124	22.1	30	17.9
$15,000-$25,000	214	24.3	198	23.9	139	24.8	39	23.2
$25,000-$50,000	296	33.6	296	35.7	204	36.4	60	35.7
≥$50,000	180	20.4	159	19.2	94	16.8	39	23.2
Unknown	126		145		95		28	
Marital status								
Married	536	54.6	517	54.4	343	53.8	103	53.4
Widowed	315	32.1	301	31.7	201	31.6	65	33.7
Divorced/separated	121	12.3	125	13.1	87	13.7	23	11.9
Single	10	1.0	8	0.8	6	0.9	2	1.0
Unknown	25		24		19		3	
Education								
Less than high school	153	15.2	126	12.9	87	13.3	19	9.7
High school graduate	395	39.3	376	38.6	251	38.3	84	42.9
Some college	286	28.4	312	32.0	210	32.0	59	30.1
College graduate	172	17.1	161	16.5	108	16.5	34	17.3
Unknown	1		0		0		0	
First-degree family history of breast cancer								
No	771	82.9	703	77.2	469	77.1	146	78.5
Yes	159	17.1	208	22.8	139	22.9	40	21.5
Unknown	77		64		48		10	
Average weekly alcohol consumption								
None	518	51.6	461	47.5	320	49.1	78	39.8
<7 drinks	317	31.6	316	32.6	203	31.1	75	38.3
≥7 drinks	169	16.8	193	19.9	129	19.8	43	21.9
Unknown	3		5		4		0	

Table 2.1, continued

Characteristic	Controls (n=1,007) n	%	All cases (n=975) n	%	Ductal (n=656) n	%	Lobular (n=196) n	%
Duration of unopposed estrogen HRT use								
Never/<6 months	533	53.3	511	52.9	350	53.9	91	46.7
6months-<5 years	145	14.5	112	11.6	78	12.0	24	12.3
≥5 years	322	32.2	343	35.5	221	34.1	80	41.0
Unknown	7		9		7		1	
Duration of combined estrogen+progestin HRT use								
Never/<6 months	836	83.5	740	76.1	506	77.4	137	70.3
6months-<5 years	60	6.0	65	6.7	46	7.0	14	7.2
≥5 years	105	10.5	167	17.2	102	15.6	44	22.6
Unknown	6		3		2		1	

Table 2.2: Relationship of reproductive factors to risk of overall and specific histologic types of breast cancer

	Controls N = 1007		Overall N = 975				Ductal N = 656				Lobular N = 196			
Reproductive Factor	**N**	**%**	**N**	**%**	**OR***	**95% CI**	**N**	**%**	**OR**	**95% CI**	**N**	**%**	**OR**	**95% CI**
Age at menarche														
8-11	173	17.2	182	18.8	**1.0**	(ref)	126	19.4	**1.0**	(ref)	35	17.9	**1.0**	(ref)
12-13	520	51.7	525	54.2	**1.0**	(0.8-1.2)	357	54.8	**0.9**	(0.7-1.2)	104	53.1	**1.0**	(0.6-1.5)
≥14	313	31.1	261	27.0	**0.8**	(0.6-1.0)	168	25.8	**0.7**	(0.5-1.0)†	57	29.1	**0.9**	(0.6-1.4)
Parity														
Nulliparous	94	9.3	88	9.0	**1.0**	(ref)	57	8.7	**1.0**	(ref)	20	10.2	**1.0**	(ref)
Parous	913	90.7	887	91.0	**1.0**	(0.8-1.4)	599	91.3	**1.1**	(0.8-1.5)	176	89.8	**0.9**	(0.5-1.5)
Number of full term births														
1	77	8.4	88	9.9	**1.0**		62	10.4	**1.0**		21	11.9	**1.0**	
2	197	21.6	258	29.1	**1.1**	(0.8-1.6)	171	28.5	**1.1**	(0.7-1.6)	49	27.8	**0.9**	(0.5-1.6)
3	271	29.7	251	28.3	**0.8**	(0.6-1.2)	164	27.4	**0.8**	(0.5-1.1)	51	29.0	**0.7**	(0.4-1.2)
≥4	368	40.3	290	32.7	**0.7**	(0.5-1.0)†	202	33.7	**0.7**	(0.5-1.0)†	55	31.3	**0.6**	(0.3-1.0)†
Age at first full term birth														
≤19	187	20.5	152	17.2	**1.0**	(ref)	98	16.4	**1.0**	(ref)	31	17.6	**1.0**	(ref)
20-24	435	47.7	432	48.9	**1.2**	(0.9-1.6)	302	50.7	**1.3**	(1.0-1.8)	84	47.7	**1.2**	(0.7-1.8)
25-29	205	22.5	206	23.3	**1.2**	(0.9-1.6)	136	22.8	**1.3**	(0.9-1.7)	41	23.3	**1.2**	(0.7-2.0)
≥30	85	9.3	93	10.5	**1.3**	(0.9-1.9)	60	10.1	**1.3**	(0.9-2.0)	20	11.4	**1.4**	(0.7-2.6)
Duration of oral contraceptive use														
Never	752	75.4	736	76.0	**1.0**	(ref)	508	78.0	**1.0**	(ref)	141	72.3	**1.0**	(ref)
<5 years	159	15.9	139	14.4	**0.9**	(0.7-1.2)	85	13.1	**0.8**	(0.6-1.1)	30	15.4	**1.1**	(0.7-1.6)
≥5 years	86	8.6	93	9.6	**1.1**	(0.8-1.5)	58	8.9	**1.0**	(0.7-1.4)	24	12.3	**1.6**	(1.0-2.6)

Table 2.2, continued

Reproductive Factor	Controls N = 1007 N	%	Overall N = 975 N	%	OR*	95% CI	Ductal N = 656 N	%	OR	95% CI	Lobular N = 196 N	%	OR	95% CI
Type of menopause‡														
Natural	596	59.9	568	59.1	**1.0**	(ref)	394	61.0	**1.0**	(ref)	109	56.8	**1.0**	(ref)
Induced	168	16.9	142	14.8	**1.0**	(0.8-1.3)	86	13.3	**0.9**	(0.6-1.2)	32	16.7	**1.4**	(0.9-2.2)
Age at menopause‡														
≤44	171	24.5	117	18.6	**1.0**	(ref)	72	16.8	**1.0**	(ref)	23	19.2	**1.0**	(ref)
45-49	191	27.3	187	29.8	**1.5**	(1.1-2.0)†	134	31.2	**1.7**	(1.2-2.5)†	31	25.8	**1.2**	(0.7-2.2)
50-54	239	34.2	232	36.9	**1.4**	(1.0-1.9)†	155	36.1	**1.5**	(1.1-2.2)†	50	41.7	**1.4**	(0.8-2.5)
≥55	98	14.0	92	14.7	**1.5**	(1.0-2.2)	68	15.9	**1.8**	(1.1-2.7)†	16	13.3	**1.2**	(0.6-2.4)

* All OR's are adjusted for age. Additionally, OR's for type of menopause are also adjusted for duration of CHRT use, and OR's for age at menopause are also adjusted for first-degree family history of breast cancer.

† p-value < 0.05

‡ Excludes women with an unknown type of menopause and/or age at menopause.

Table 2.3: Relationship of anthropometric factors to risk of overall and specific histologic types of breast cancer

Anthropometric Factor	Controls N = 1007		Overall N = 975				Ductal N = 656				Lobular N = 196			
	N	%	N	%	OR	95% CI	N	%	OR	95% CI	N	%	OR	95% CI
Height, cm														
<160	226	22.5	162	16.7	**1.0**	(ref)	113	17.3	**1.0**	(ref)	30	15.3	**1.0**	(ref)
160-164	264	26.2	292	30.0	**1.6**	(1.2-2.1)†	192	29.3	**1.5**	(1.1-2.0)†	61	31.1	**2.0**	(1.2-3.4)†
165-169	294	29.2	274	28.2	**1.4**	(1.0-1.8)†	179	27.3	**1.3**	(0.9-1.8)†	60	30.6	**1.9**	(1.1-3.2)†
≥170	222	22.1	244	25.1	**1.6**	(1.2-2.1)†	171	26.1	**1.6**	(1.2-2.2)†	45	23.0	**1.8**	(1.0-3.1)†
Weight														
≤130	289	29.1	216	22.4	**1.0**	(ref)	145	22.4	**1.0**	(ref)	49	25.1	**1.0**	(ref)
131-149	204	20.5	223	23.1	**1.5**	(1.1-1.9)†	147	22.7	**1.4**	(1.1-1.9)†	50	25.6	**1.5**	(0.9-2.2)
150-174	272	27.4	265	27.5	**1.3**	(1.0-1.7)†	181	27.9	**1.3**	(1.0-1.7)†	47	24.1	**1.0**	(0.7-1.6)
≥175	228	23.0	260	27.0	**1.5**	(1.2-2.0)†	175	27.0	**1.5**	(1.2-2.0)†	49	25.1	**1.3**	(0.8-2.0)
Weight at age 30														
≤118	255	25.6	235	24.3	**1.0**	(ref)	146	22.5	**1.0**	(ref)	55	28.1	**1.0**	(ref)
119-128	283	28.4	258	26.7	**1.0**	(0.8-1.3)	166	25.6	**1.0**	(0.8-1.4)	61	31.1	**1.0**	(0.7-1.5)
129-139	211	21.2	226	23.4	**1.2**	(0.9-1.5)	156	24.1	**1.3**	(1.0-1.7)	37	18.9	**0.8**	(0.5-1.3)
≥140	247	24.8	247	25.6	**1.1**	(0.8-1.4)	180	27.8	**1.3**	(1.0-1.7)	43	21.9	**0.8**	(0.5-1.2)
Maximum weight														
≤140	287	28.6	231	23.8	**1.0**	(ref)	151	23.1	**1.0**	(ref)	54	27.6	**1.0**	(ref)
141-160	264	26.3	258	26.6	**1.2**	(1.0-1.6)	180	27.5	**1.3**	(1.0-1.7)	45	23.0	**0.9**	(0.6-1.4)
161-184	209	20.9	236	24.3	**1.4**	(1.1-1.8)†	156	23.9	**1.4**	(1.1-1.8)†	47	24.0	**1.2**	(0.8-1.8)
≥185	242	24.2	246	25.3	**1.3**	(1.0-1.6)	167	25.5	**1.3**	(1.0-1.6)	50	25.5	**1.1**	(0.7-1.7)
BMI, quartiles														
≤23.32	261	27.1	209	22.3	**1.0**	(ref)	139	22.0	**1.0**	(ref)	51	27.1	**1.0**	(ref)
23.33-26.20	241	25.0	240	25.6	**1.3**	(1.0-1.7)	164	25.9	**1.3**	(1.0-1.8)	43	22.9	**0.9**	(0.6-1.5)
26.21-30.11	230	23.9	245	26.1	**1.4**	(1.1-1.9)†	162	25.6	**1.5**	(1.1-2.0)†	52	27.7	**1.2**	(0.8-1.9)
≥30.12	231	24.0	245	26.1	**1.4**	(1.0-1.8)†	168	26.5	**1.4**	(1.0-1.9)†	42	22.3	**1.0**	(0.6-1.6)

* All OR's are adjusted for age, and OR's for height and BMI are also adjusted for income.

† p-value < 0.05

NOTES TO CHAPTER 2

1. Newcomer LM, Newcomb PA, Daling JR, Yasui Y, Potter JD. Post-menopausal hormone use and risk of breast cancer by histologic type. Am J Epidemiol 1999;149:S79.
2. Li CL, Weiss NS, Stanford JL, Daling JR. Hormone replacement therapy in relation to risk of lobular and ductal breast carcinoma in middle-aged women. Cancer 2000;88:2570-2577.
3. Chen CL, Weiss NS, Newcomb P, Barlow W, White E. Hormone replacement therapy in relation to breast cancer. JAMA 2002;287:734-741.
4. Newcomb PA, Titus-Ernstoff L, Egan KM, et al. Postmenopausal estrogen and progestin use in relation to breast cancer risk. Cancer Epidemiol Biomarker Prev 2002;11:593-600.
5. Daling JR, Malone KE, Doody DR, et al. Relation of Regimens of Combined Hormone Replacement Therapy to Lobular, Ductal, and Other Histologic Types of Breast Carcinoma. Cancer 2002;in press.
6. Stierer M, Rosen H, Weber R, Hanak H, Spona J, Tuchler H. Immunohistochemical and biochemical measurement of estrogen and progesterone receptors in primary breast cancer: Correlation of histopathology and prognostic factors. Ann Surg 1993;218:13-21.
7. Stalsberg H, Thomas DB, Noonan EA, The WHO Collaborative Study of Neoplasia and Steroid Contraceptives. Histologic types of breast carcinoma in relation to international variation and breast cancer risk factors. Int J Cancer 1989; 44: 399-409.
8. Li CL, Anderson BO, Porter P, Holt SK, Daling JR, Moe RE. Changing incidence rate of invasive lobular breast carcinoma among older women. Cancer 2000;88:2561-2569.
9. Bernstein L. The epidemiology of breast cancer. Women Cancer 1998;1S:7-13.
10. Breslow NE, Day NE. The Analysis of Case-Control Studies. Lyon, France: International Agency for Research on Cancer; 1980.
11. Begg CB, Gray R. Calculation of polychotomous logistic regression parameters using individualized regressions. Biometrika 1984;71:11-18.

12. Daling JR, Malone KE, Doody DR, Johnson LG, Gralow JR, Porter PL. Relation of body mass index to tumor markers and survival among young women with invasive ductal breast carcinoma. Cancer 2001;92:720-729.

13. Azzopardi GJ. Problems in Breast Pathology (1st ed). Eastbourne: WB Saunders, 1979; Chapter 11: 240-257.

14. Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and hormonal contraceptives. Lancet 1996;347:1713-1727.

15. Oyama T, Kashiwabara K, Yoshimoto K, Arnold A, Koerner F. Frequent overexpression of the cyclin D1 oncogene in invasive lobular carcinoma of the breast. Cancer Res 1998;58:2876-2880.

16. Lee AH, Dublin EA, Bobrow LG, Poulsom R. Invasive lobular and invasive ductal carcinoma of the breast show distinct patterns of vascular endothelial growth factor expression and angiogenesis. J Pathol 1998;185:394-401.

17. Acs G, Lawton TJ, Rebbeck TR, LiVolsi VA, Zhang PJ. Differential expression of E-cadherin in lobular and ductal neoplasms of the breast and its biologic and diagnostic implications. Am J Clin Pathol 2001;115:85-98.

CHAPTER 3:

The relationship between alcohol use and risk of breast cancer by histology and hormone receptor status among women 65-79 years of age

ABSTRACT

Background: Alcohol consumption is associated with a moderate increase in breast cancer risk, possibly because alcohol increases estrogen levels. Certain types of breast carcinomas are more hormonally responsive than others, including those that have a lobular histology or are hormone receptor positive, but few studies evaluating alcohol use and risk of breast cancer have stratified their results by histologic type or estrogen receptor (ER)/progesterone receptor (PR) status.

Methods: A population-based case-control study of women 65-79 years of age was conducted in western Washington State. The responses of 975 women diagnosed with invasive breast cancer during 1997-1999 were compared to those of 1,007 controls. Associations between alcohol use and breast cancer risk by histology and hormone receptor status were evaluated using polytomous regression.

Results: Ever use of alcohol over the past 20 years was associated with a 1.3-fold (95% confidence interval (CI): 1.0-1.5) increased risk of breast cancer, though this increase was primarily limited to women who consumed ≥30.0 g/day of alcohol (OR=1.7, 95% CI: 1.1-2.6). Differences in risk by histology were observed as ever use of alcohol was associated with a 1.8-fold (95% CI: 1.3-2.5) increased risk of lobular cancer, but only a 1.2-fold (95% CI: 0.9-1.4) increased risk of ductal cancer. Also, differences by hormone receptor status were found as ever users of alcohol had an increase in risk of ER-positive/PR-positive tumors (OR=1.3, 95% CI: 1.1-1.7), but no change in their risk of ER-positive/PR-negative or ER-negative/PR-negative tumors (OR=1.1, 95% CI: 0.7-1.5 and OR=1.1, 95% CI: 0.7-1.7, respectively).

Conclusions: Alcohol use appears to be more strongly associated with risk of lobular carcinomas and hormone receptor positive tumors than it is with other types of breast cancer. These results suggest that alcohol is involved in the etiology of breast cancers that are hormonally sensitive.

INTRODUCTION

Reviews and meta-analyses of observational studies evaluating alcohol use and breast cancer risk have consistently shown that alcohol use is a moderate risk factor for breast cancer.[1-3] Specifically, a recent meta-analysis of 42 studies reported that use of 12 g/day and 24 g/day of alcohol are associated with 10% (95% CI: 6%-14%) and 21% (95% CI: 13%-30%) elevations in risk of breast cancer, respectively.[2]

One of the mechanisms thought to underlie this association is the influence that alcohol use has on hormone levels in women.[1] In breast cancer cells in culture, ethanol has been shown to stimulate the proliferation of estrogen receptor positive (ER+), but not estrogen receptor-negative (ER-) cells.[4,5] A controlled feeding study of healthy postmenopausal women demonstrated that alcohol consumption increases estrone sulfate and dehydroepiandrosterone (DHEA) concentrations in a dose dependent manner.[6] Thus, one might expect that alcohol use may selectively increase a woman's risk of hormonally responsive breast cancers. However, epidemiologic data from five studies investigating the relationship between alcohol use and risk of breast tumors with different hormone receptor profiles are inconsistent. Two of these studies found that alcohol use increased risk of ER+ but not ER- breast cancers,[7,8] one found that it only increased risk of ER-/progesterone receptor-negative (PR-) breast cancer,[9] and two found that a woman's risk of ER+ and ER- breast cancer did not differ by alcohol use.[10,11] The fact that alcohol use is but a moderate risk factor for breast cancer may account for these inconsistencies, though further investigation of these relationships is warranted.

There is also growing evidence that the hormonal responsiveness of tumors varies by histologic type. For example, invasive lobular carcinoma (ILC), the second most common histologic type of breast cancer, is more likely to be both ER+ and progesterone receptor-positive (PR+) compared to the most common histologic type of breast cancer, invasive ductal carcinoma (IDC).[12] Five recent studies also report that use of combined estrogen and progestin hormone replacement therapy (HRT) is associated with a 2.0 to 3.9-fold increased risk of ILC, but has little impact on risk of IDC.[13-17] However, only one small study has evaluated the relationship between alcohol use and risk of breast cancer of different histologies.[8] It found that use of ≥15 g/day of alcohol was associated with a 1.76-fold (95% CI: 0.83-3.71) increased risk of ILC, but with only a 1.32-fold (95% CI: 1.01-1.72) increased risk of IDC.

Using data from a population-based case-control breast cancer study, we assessed the relationship between alcohol use and risk of invasive breast cancer by histology and hormone receptor status.

METHODS

We conducted a population-based case-control study of women 65-79 years of age living in the three county Seattle-Puget Sound metropolitan area. Study interviewers conducted in-person interviews on all subjects.

Cases:

Women aged 65-79 years with no prior history of *in-situ* or invasive breast cancer when diagnosed with invasive breast cancer between April 1, 1997 and May 31, 1999, were eligible as cases. The Cancer Surveillance System (CSS), the population-based tumor registry that serves the Seattle-Puget Sound region of Washington State and participates in the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute, was used to identify cases. In order to be eligible for the study, all cases had to live in King, Pierce, or Snohomish counties and have a Health Care Financing Administration (HCFA) record, since

these records were used to identify controls. Of the 1,210 eligible cases identified and selected, 975 (80.6%) were interviewed.

Information on tumor histology and hormone receptor status was ascertained from CSS, which abstracts data on tumor characteristics from medical records and pathology reports from institutions serving the area. CSS classifies histology using the International Classification of Diseases for Oncology (ICD-O) codes, and we divided cases into two groups with codes 8520 and 8522 used to define the 196 ILC cases and code 8500 used to define the 656 IDC cases. The 123 women with other breast cancer histologies were excluded from our analyses by histologic type. CSS classifies ER and PR status as positive, negative, borderline, not assessed, or unknown based on information abstracted from medical records. The 75 (7.7%) cases with an ER and/or PR status that was borderline, not assessed, or unknown were excluded from our analyses by hormone receptor status. Additionally, we did not include ER-/PR+ cases in our analysis of joint ER/PR status because there were only 6 cases with this ER/PR profile.

Controls:

HCFA records were used to identify women from the general population of female residents of King, Pierce, and Snohomish counties who were the same ages as cases to serve as controls. Of the 1,365 eligible women selected as controls, 1,007 (73.8%) were interviewed. Controls were assigned reference dates, the distribution of which was similar to that of the diagnosis dates of cases.

Data Collection

Informed consent was obtained from all study subjects. Both cases and controls were interviewed in-person and were asked about menstrual, contraceptive and reproductive histories, use of HRT, body size, and medical history, including family history of cancer. Demographic data and information on smoking status were also ascertained.

Information on alcohol use over the past 20 years was collected. Drinkers included women who reported that they had consumed at least 12 beverages containing alcohol during the

past 20 years and had consumed at least one alcohol-containing beverage a month for 6 months or more during the past 20 years. A woman's age 20 years prior to her reference date defined the beginning of her first drinking interval. Women were asked separate questions about frequency of consumption (times per day, week, month, or year) of beer (12-ounce bottle or can), wine (4-ounce glass), and liquor (1.5-ounce shot). After reporting their use of these three types of alcoholic beverages, they were asked at what age their drinking habits changed. If this age was prior to reference age it marked the beginning of a second drinking interval, and the previous questions were repeated until women reported no further changes in their drinking habits.

Analysis

We compared all breast cancer cases to controls using unconditional logistic regression.[18] We compared ILC and IDC cases to controls, and cases with different hormone receptor profiles to controls using polytomous logistic regression.[19] Both statistical approaches were used to calculate odds ratios (ORs) as an estimate of the relative risk and to compute 95% confidence intervals (CIs). In order to convert intake of beer, wine, and liquor into average daily grams of alcohol consumed over the past 20 years, the frequency with which each beverage was consumed was multiplied by the ethanol content of each beverage as estimated by the United States Department of Agriculture (13.2 g per 12 oz bottle or can of beer, 10.8 g per 4 oz glass of wine, and 15.1 g per 1 oz drink or shot of liquor).[20] Alcohol intake in grams per day was then categorized into six groups, none, <1.5, 1.5-4.9, 5.0-14.9, 15.0-29.9, and ≥30.0, consistent with previously published categorizations of alcohol use.[21,22]

The following variables were evaluated as potential confounders and effect modifiers: first-degree family history of breast cancer (yes/no); education (less than high school, high school graduate, some college, college graduate or higher); type of menopause (natural, induced, simple hysterectomy (hysterectomy without a bilateral oophorectomy)) and age at menopause (five-year categories). Also evaluated were age at menarche (≤11, 12-13, ≥14); parity; age at first full-term (>26 weeks) pregnancy (14-19, 20-24, 25-29, ≥30 years); body mass index (BMI) five years prior

to reference date (quartiles of control population); smoking status (never, former, current); oral contraceptive use (never, <5 years, ≥5 years); and HRT use (never/<6 months, 6 months to <5 years, ≥5 years). Only adjustment for family history of breast cancer and BMI changed the risk estimates of the odds ratios of interest by more than 10%. Therefore, all analyses were adjusted for age (continuous), first-degree family history of breast cancer (yes/no), and BMI (quartiles). BMI was also found to be an effect modifier of the relationship between alcohol use and risk of breast cancer by histology (but not of the relationship between alcohol use and risk of breast cancer by hormone receptor status). Thus, we stratified this analysis by BMI dividing women into those with a BMI less than or greater than the median BMI among controls (26.2 kg/m^2), and adjusting for age (continuous), family history of breast cancer (yes/no), and BMI (continuous) in each of these analyses. All p-values for linear trend were estimated using grams/day of alcohol use as a continuous term in each model and excluding women who were never users of alcohol.

RESULTS

Lobular, ductal, and ER+ cases had a similar age distribution as controls, but ER- cases tended to be younger than controls (Table 3.1). Controls were more likely than cases to be non-white. ILC cases had higher incomes compared to both controls and the other case groups. Women in each case group were more likely to have had a hysterectomy without a bilateral oophorectomy and to have a first-degree family history of breast cancer compared to controls. Both IDC and ER+ cases were somewhat more likely than controls to have a higher body mass index (BMI). All cases were more likely to be former or current smokers and to have ever used HRT for 5 years or longer, with the ILC case group having the highest proportion of HRT users.

Ever use of alcohol was associated with a 1.3-fold (95% CI: 1.0-1.5) increased risk of breast cancer. Though women who consumed ≥30.0 g/day of alcohol had the highest risk of breast cancer (OR=1.7, 95% CI: 1.1-2.6), no linear trend was observed (p for trend = 0.673) (Table 3.2). When examined by histology, ever use of alcohol was associated with an increased

risk of ILC, but not IDC (OR=1.8, 95% CI: 1.3-2.5 and OR=1.2, 95% CI: 0.9-1.4, respectively). Women who used ≥30.0 g/day of alcohol had the highest risk of ILC (OR=2.6, 95% CI: 1.3-4.9), but again no linear trend was observed (p for trend = 0.614).

BMI was found to modify the relationship between alcohol use and risk of breast cancer by histology (Table 3.3). In our stratified analysis, ever use of alcohol was only associated with an increased risk of ILC among women with a BMI >26.20 kg/m^2 (OR=2.5, 95% CI: 1.5-4.0). Within this group of women, those who used ≥30.0 g/day of alcohol had a 4.8-fold (95% CI: 2.0-11.4) increased risk of ILC, but risk did not increase as the amount of alcohol consumed increased (p for trend = 0.340). Risks of all histologic types of breast cancer and IDC were somewhat elevated among ever users of alcohol for women in both BMI subgroups, but these elevations in risk were all within the limits of chance.

Ever use of alcohol was associated with elevations in risk of ER+ and PR + tumors (OR=1.3, 95% CI: 1.0-1.6 and OR=1.3, 95% CI: 1.1-1.7, respectively), but did not alter risks of ER- and PR- tumors (OR=1.1, 95% CI: 0.7-1.7 and OR=1.1, 95% CI: 0.8-1.4, respectively). The greatest elevations in risk of ER+ and PR+ tumors were seen among women who used ≥30.0 g/day of alcohol (OR=1.7, 95% CI: 1.1-2.7 and OR=1.8, 95% CI: 1.1-2.8, respectively), though no linear trends were observed. Similarly, ever use of alcohol was associated with an elevation in risk of ER+/PR+ tumors (OR=1.3, 95% CI: 1.1-1.7), but not with elevations in risk of ER+/PR- or ER-/PR- tumors (OR=1.1, 95% CI: 0.7-1.5 and OR=1.1, 95% CI: 0.7-1.7, respectively).

DISCUSSION

Certain limitations of our study should be considered when interpreting our results. We did not conduct independent pathology reviews or test all tumors for hormone receptor status in our institution. Instead we relied on the assessments made by the numerous pathologists and laboratories serving the Seattle-Puget Sound area. Misclassification of tumor histology and hormone receptor status may have resulted. We were also limited by a relatively small number of

ILC cases, preventing us from having the power to assess the effects of different types of alcohol or of recency of alcohol use on risk of breast cancer by histologic type.

Additionally, we interviewed only 80.6% of all eligible cases and 73.8% of all eligible controls. Our results could be biased if the women we were unable to interview differed from those who did participate with regard to their use of alcohol. We also relied on participants' recall of their alcohol use over the past 20 years. However, it has been documented that the recall bias associated with data on alcohol use collected retrospectively from both cases and controls has minimal effects on alcohol risk estimates when compared to prospectively collected data.[23]

Alcohol consumption has been shown to be a moderate but consistent risk factor for breast cancer in both observational studies and meta-analyses,[1-3] and in the present study we confirm this association. The influence alcohol has on increasing hormone levels, particularly estrone sulfate and DHEA, is believed to be one of the mechanisms underlying this association.[1] Consistent with this mechanism, we found that alcohol consumption, particularly heavy alcohol consumption (≥30.0 g/day), is primarily associated with breast cancers that are particularly hormone sensitive, both ILC and ER+/PR+ tumors.

While our results certainly need to be confirmed by others, data from the one study that has evaluated the relationship between alcohol use and risk of ILC and IDC were suggestive of a similar difference by histology, though this study included a limited number of ILC cases.[8] This finding is particularly interesting in light of recent studies demonstrating that use of combined estrogen and progestin HRT is more strongly associated with risk of ILC than it is with risk of IDC. Our data suggest that alcohol use may be another hormonally related risk factor for breast cancer that exerts a stronger effect on risk of ILC than it does on risk of IDC.[13-17] However, the studies evaluating HRT did not find that the use of unopposed estrogen increased risk of either ILC or IDC. Taken together then, the available evidence suggests that combined estrogen and progestin HRT use and the intake of alcohol, which increases endogenous estrogen levels, appear to increase ILC risk, while the use of exogenous estrogens without progestin does not.

While seemingly contradictory results, these data point to a need for further studies to more clearly elucidate the complex interactions that exist between hormones, and between hormones and alcohol, and how they influence lobular carcinogenesis.

We did identify an interaction between alcohol use and BMI with respect to ILC risk. If the influence alcohol has on hormonal levels is what accounts for the elevated risk of ILC associated with alcohol use, this result is not surprising given that both alcohol use and having a high BMI are associated with elevated hormone levels,[24] including estrogen sulfate, the most abundant form of estrogen in postmenopausal women.[25] Thus, women who drink alcohol and are obese may be expected to have particularly high endogenous estrogen levels, and this may account for their elevated risk of ILC. However, this is the only study to document this finding so we encourage other investigators who have examined the relationship between alcohol use and breast cancer risk to stratify their results by histology and to examine the impact that potential effect modifiers may have.

We also found that ever use of alcohol, and particularly heavy use of alcohol, is associated with an elevation in risk of hormone receptor positive tumors, while it is not associated with risk of hormone receptor negative tumors. The other studies evaluating this association have been inconclusive with two studies finding that alcohol use increases risk of ER+ but not ER- breast cancers,[7,8] one finding that it only increases risk of ER-/PR- breast cancer,[9] and two finding that risk of ER+ and ER- breast cancer did not differ by alcohol use.[10,11] However, one of the strengths of our study is that data on ER/PR status were missing for only 7.7% of cases, while 16%-60% of the cases in these other studies had missing data on ER and/or PR status, and four of these five studies had data missing on greater than 25% of cases. Additionally, these inconsistencies may be due to the fact that the magnitude of the increase in breast cancer risk associated with alcohol use is modest. Despite the inconsistencies within the epidemiologic literature, data from our study and others suggest that heavy alcohol use is associated with an increased risk of hormone receptor positive tumors. There is laboratory evidence supporting

these results as ethanol has been shown to stimulate the proliferation of estrogen receptor positive (ER+), but not estrogen receptor-negative (ER-), breast cancer cells in culture.[4,5]

Taken as a whole, our results add to the evidence that alcohol is likely involved in pathways contributing to hormonal carcinogenesis of the breast. We found that alcohol use, particularly heavy alcohol use, increases risk of ILC and hormone receptor positive tumors. Breast cancer is a heterogeneous disease, and further research focusing on different types of breast cancer is a valuable approach toward gaining a clearer understanding of mechanisms involved in breast carcinogenesis.

Table 3.1: Distribution of demographic and known risk factors for breast cancer among 1,007 controls, 975 breast cancer cases, 656 ductal cases, 196 lobular cases, 796 ER-positive cases, and 107 ER-negative cases

	Controls (n=1,007)		All cases (n=975)		Ductal (n=656)		Lobular (n=196)		ER-positive (n=796)		ER-negative (n=107)	
Characteristic	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Reference age												
65-69	330	32.8	300	30.8	204	31.1	58	29.6	240	30.2	41	38.3
70-74	381	37.8	381	39.1	252	38.4	85	43.4	319	40.1	33	30.8
75-79	296	29.4	294	30.2	200	30.5	53	27.0	237	29.8	33	30.8
Race												
White	925	91.9	929	95.3	623	95	188	95.9	759	95.4	104	97.2
Black	37	3.7	16	1.6	11	1.7	3	1.5	13	1.6	2	1.9
Asian/PI	29	2.9	19	1.9	18	2.7	1	0.5	17	2.1	0	0.0
Other/unknown	16	1.6	11	1.1	4	0.6	4	2.0	7	0.9	1	0.9
Income												
<$15,000	191	21.7	177	21.3	124	22.1	30	17.9	145	21.3	22	24.4
$15-25,000	214	24.3	198	23.9	139	24.8	39	23.2	166	24.4	20	22.2
$25-50,000	296	33.6	296	35.7	204	36.4	60	35.7	239	35.1	36	40.0
>$50,000	180	20.4	159	19.2	94	16.8	39	23.2	131	19.2	12	13.3
Missing	126		145		95		28		115		17	
Parity												
Nulliparous	94	9.3	88	9.0	57	8.7	20	10.2	71	8.9	11	10.3
Parous	913	90.7	887	91.0	599	91.3	176	89.8	725	91.1	96	89.7
Type of menopause												
Natural	607	61.6	583	61.4	400	62.8	113	59.8	483	62.6	58	55.2
Induced	148	15.0	129	13.6	78	12.2	29	15.3	96	12.4	18	17.1
Simple hysterectomy	231	21.6	237	25.0	159	25.0	47	24.9	193	25.0	29	27.6
Missing	21		26		19		7		24		2	

Table 3.1, continued

Characteristic	Controls (n=1,007)		All cases (n=975)		Ductal (n=656)		Lobular (n=196)		ER-positive (n=796)		ER-negative (n=107)	
	N	%	N	%	N	%	N	%	N	%	N	%
First degree family history of breast cancer												
No	771	82.9	703	77.2	469	77.1	146	78.5	564	76.0	83	82.2
Yes	159	17.1	208	22.8	139	22.9	40	21.5	178	24.0	18	17.8
Missing	77		64		48		10		54		6	
BMI, quartiles												
≤23.32	261	27.1	209	22.3	139	22.0	51	27.1	166	21.6	25	24.3
23.33-26.20	241	25.0	240	25.6	164	25.9	43	22.9	196	25.5	28	27.2
26.21-30.11	230	23.9	245	26.1	162	25.6	52	27.7	200	26.0	26	25.2
≥30.12	231	24.0	245	26.1	168	26.5	42	22.3	206	26.8	24	23.3
Missing	44		36		23		8		28		4	
Ever use of HRT												
Never/<6 months	413	41.1	352	36.3	243	37.3	59	30.1	285	35.9	40	38.1
6 months-5 years	156	15.5	119	12.3	87	13.4	22	11.2	97	12.2	16	15.2
≥5 years	435	43.3	499	51.4	321	49.3	115	58.7	411	51.8	49	46.7
Missing	3		5		5		0		3		2	
Smoking status												
Never	523	51.9	450	46.2	301	45.9	89	45.4	373	46.9	48	44.9
Former	369	36.6	396	40.6	269	41.0	79	40.3	321	40.3	46	43.0
Current	115	11.4	129	13.2	86	13.1	28	14.3	102	12.8	13	12.1

Table 3.2: Relationship between alcohol use and risk of overall and specific histologic types of breast cancer

	Controls N = 998		Overall N = 967				Ductal N = 651				Lobular N = 195			
Factor	**N**	**%**	**N**	**%**	**OR***	**95% CI**	**N**	**%**	**OR**	**95% CI**	**N**	**%**	**OR**	**95% CI**
Alcohol use (g/day)														
Never†	514	51.5	459	47.5	**1.0**	(ref)	319	49.0	**1.0**	(ref)	77	39.5	**1.0**	(ref)
Ever	484	48.5	508	52.5	**1.3**	(1.0-1.5)‡	332	51.0	**1.2**	(0.9-1.4)	118	60.5	**1.8**	(1.3-2.5)‡
<1.5	59	5.9	60	6.2	**1.2**	(0.8-1.8)	41	6.3	**1.2**	(0.8-1.9)	14	7.2	**1.5**	(0.8-3.0)
1.5-4.9	121	12.2	128	13.2	**1.6**	(0.9-1.7)	85	13.0	**1.2**	(0.9-1.7)	31	15.9	**1.9**	(1.2-3.1)‡
5.0-14.9	167	16.6	161	16.6	**1.1**	(0.9-1.5)	100	15.4	**1.0**	(0.7-1.3)	36	18.5	**1.6**	(1.0-2.5)‡
15.0-29.9	91	9.2	96	9.9	**1.3**	(0.9-1.7)	68	10.4	**1.2**	(0.9-1.8)	20	10.3	**1.7**	(1.0-2.9)
≥30.0	46	4.6	63	6.5	**1.7**	(1.1-2.6)‡	38	5.8	**1.5**	(0.9-2.3)	17	8.7	**2.6**	(1.3-4.9)‡
***p* for trend§**					**0.673**				**0.931**				**0.614**	

* All odds ratios (ORs) are adjusted for age (continuous), family history of breast cancer (yes/no), and body mass index (quartiles).

† Women who drank <12 beverages containing alcohol during the past 20 years, or who did not consume at least one beverage containing alcohol a month for 6 months during the past 20 years, were classified as never users of alcohol.

‡ $p < 0.05$.

§ p-values for trend were evaluated by treating alcohol use (g/day) as a continuous variable and excluding subjects who were never users of alcohol.

Table 3.3: Relationship between alcohol use and risk of overall and specific histologic types of breast cancer by body mass index

	Body mass index ≤26.20 kg/m^2													
	Controls N = 500		All cases N = 446				Ductal N = 301				Lobular N = 94			
Factor	**N**	**%**	**N**	**%**	**OR***	**95% CI**	**N**	**%**	**OR**	**95% CI**	**N**	**%**	**OR**	**95% CI**
Alcohol use (g/day)														
Never	222	44.4	179	40.1	**1.0**	(ref)	119	39.5	**1.0**	(ref)	36	38.3	**1.0**	(ref)
Ever	278	55.6	267	59.9	**1.2**	(0.9-1.6)	182	60.5	**1.3**	(0.9-1.7)	58	61.7	**1.3**	(0.8-2.1)
<1.5	27	5.4	22	4.9	**1.1**	(0.6-2.0)	18	6.0	**1.3**	(0.7-2.6)	2	2.1	**0.5**	(0.1-2.2)
1.5-4.9	68	13.6	65	14.6	**1.2**	(0.8-1.8)	45	15.0	**1.3**	(0.8-2.0)	17	18.1	**1.6**	(0.8-3.0)
5.0-14.9	99	19.8	88	19.7	**1.2**	(0.8-1.7)	52	17.3	**1.0**	(0.7-1.6)	22	23.4	**1.4**	(0.8-2.6)
15.0-29.9	56	11.2	54	12.1	**1.2**	(0.8-1.9)	42	14.0	**1.4**	(0.9-2.3)	10	10.6	**1.2**	(0.5-2.5)
≥30.0	28	5.6	38	8.5	**1.8**	(1.0-3.1)	25	8.3	**1.8**	(1.0-3.4)	7	7.4	**1.3**	(0.4-3.6)
***p* for trend**					**0.408**				**0.362**				**0.673**	

	Body mass index >26.20 kg/m^2													
	Controls N = 498		All cases N = 521				Ductal N = 350				Lobular N = 101			
Factor	**N**	**%**	**N**	**%**	**OR***	**95% CI**	**N**	**%**	**OR**	**95% CI**	**N**	**%**	**OR**	**95% CI**
Alcohol use (g/day)														
Never	292	58.6	280	53.7	**1.0**	(ref)	200	57.1	**1.0**	(ref)	41	40.6	**1.0**	(ref)
Ever	206	41.4	241	46.3	**1.3**	(1.0-1.7)	150	42.9	**1.1**	(0.8-1.5)	60	59.4	**2.5**	(1.5-4.0)†
<1.5	32	6.4	38	7.3	**1.3**	(0.8-2.2)	23	6.6	**1.1**	(0.6-2.1)	12	11.9	**2.7**	(1.2-6.0)†
1.5-4.9	53	10.6	63	12.1	**1.4**	(0.9-2.1)	40	11.4	**1.2**	(0.7-1.9)	14	13.9	**2.3**	(1.1-4.7)†
5.0-14.9	68	13.7	73	14.0	**1.2**	(0.8-1.7)	48	13.7	**1.0**	(0.7-1.6)	14	13.9	**1.7**	(0.9-3.6)
15.0-29.9	35	7.0	42	8.1	**1.3**	(0.8-2.2)	26	7.4	**1.0**	(0.6-1.9)	10	9.9	**2.5**	(1.1-5.5)†
≥30.0	18	3.6	25	4.8	**1.6**	(0.8-3.1)	13	3.7	**1.1**	(0.5-2.4)	10	9.9	**4.8**	(2.0-11.4)†
***p* for trend**					**0.871**				**0.418**				**0.340**	

* All odds ratios (ORs) are adjusted for age (continuous), family history of breast cancer (yes/no), and BMI (continuous).
† $p < 0.05$

Table 3.4: Relationship between alcohol use and risk of breast cancer by ER and PR status

	Controls N = 998		ER+ N = 789				ER- N = 106				PR+ N = 648				PR- N = 244			
Factor	**N**	**%**	**N**	**%**	**OR***	**95% CI**	**N**	**%**	**OR**	**95% CI**	**N**	**%**	**OR**	**95% CI**	**N**	**%**	**OR**	**95% CI**
Alcohol use (g/day)																		
Never	514	51.5	370	47.0	**1.0**	(ref)	53	50.0	**1.0**	(ref)	300	46.3	**1.0**	(ref)	122	49.8	**1.0**	(ref)
Ever	484	48.5	419	53.1	**1.3**	(1.0-1.6)†	53	50.0	**1.1**	(0.7-1.7)	348	53.7	**1.3**	(1.1-1.7)†	122	50.0	**1.1**	(0.8-1.4)
<1.5	59	5.9	48	6.1	**1.2**	(0.8-1.8)	6	5.7	**1.1**	(0.4-2.7)	41	6.3	**1.2**	(0.8-1.9)	13	5.3	**1.0**	(0.5-1.9)
1.5-4.9	121	12.2	109	13.8	**1.6**	(1.0-1.8)	12	11.3	**1.1**	(0.5-2.1)	92	14.2	**1.4**	(1.0-2.0)†	29	11.9	**1.0**	(0.6-1.6)
5.0-14.9	167	16.6	133	16.9	**1.2**	(0.9-1.6)	18	17.0	**1.0**	(0.6-1.9)	107	16.5	**1.2**	(0.9-1.6)	43	17.6	**1.1**	(0.7-1.6)
15.0-29.9	91	9.2	76	9.6	**1.2**	(0.9-1.8)	12	11.3	**1.4**	(0.7-2.7)	65	10.0	**1.3**	(0.9-1.9)	22	9.0	**1.1**	(0.6-1.8)
≥30.0	46	4.6	53	6.7	**1.7**	(1.1-2.7)†	5	4.7	**1.2**	(0.5-3.2)	43	6.6	**1.8**	(1.1-2.8)†	15	6.1	**1.4**	(0.7-2.7)
***p* for trend**					**0.705**				**0.544**				**0.998**				**0.702**	

	Controls N = 998		ER+/PR+ N = 642				ER+/PR- N = 144				ER-/PR- N = 100			
Factor	**N**	**%**	**N**	**%**	**OR***	**95% CI**	**N**	**%**	**OR**	**95% CI**	**N**	**%**	**OR**	**95% CI**
Alcohol use (g/day)														
Never	514	51.5	298	46.4	**1.0**	(ref)	71	49.3	**1.0**	(ref)	51	51.0	**1.0**	(ref)
Ever	484	48.5	344	53.6	**1.3**	(1.1-1.7)†	73	50.7	**1.1**	(0.7-1.5)	49	49.0	**1.1**	(0.7-1.7)
<1.5	59	5.9	41	6.4	**1.2**	(0.8-1.9)	7	4.9	**0.9**	(0.4-2.1)	6	6.0	**1.1**	(0.5-2.7)
1.5-4.9	121	12.2	90	14.0	**1.4**	(1.0-2.0)†	19	13.2	**1.0**	(0.6-1.8)	10	10.0	**0.9**	(0.4-1.9)
5.0-14.9	167	16.6	106	16.5	**1.2**	(0.9-1.6)	26	18.1	**1.1**	(0.7-1.9)	17	17.0	**1.0**	(0.5-1.8)
15.0-29.9	91	9.2	64	10.0	**1.3**	(0.9-1.9)	11	7.6	**0.9**	(0.4-7.8)	11	11.0	**1.3**	(0.6-2.6)
≥30.0	46	4.6	43	6.7	**1.8**	(1.1-2.8)†	10	6.9	**1.5**	(0.7-3.3)	5	5.0	**1.2**	(0.5-3.3)
***p* for trend**					**0.945**				**0.330**				**0.656**	

* All odds ratios (ORs) are adjusted for age (continuous), family history of breast cancer (yes/no), and body mass index (quartiles).
† $p < 0.05$

NOTES TO CHAPTER 3

1. Singletary KW, Gapstur SM. Alcohol and breast cancer: review of epidemiologic and experimental evidence and potential mechanisms. JAMA 2001;286:2143-151.
2. Ellison RC, Zhang Y, McLennan CE, Rothman KJ. Exploring the relation of alcohol consumption to risk of breast cancer. Am J Epidemiol 2001;154:740-747.
3. Smith-Warner SA, Spiegelman D, Yaun S-S, et al. Alcohol and breast cancer in women: a pooled analysis of cohort studies. JAMA 1998;279:535-540.
4. Fan S, Meng Q, Gao B, Grossman J, Yadegari M, Goldberg ID, Rosen EM. Alcohol Stimulates Estrogen Receptor Signaling in Human Breast Cancer Cell Lines. Cancer Res 2000;60:5635-5639.
5. Singletary K, Frey R, Yan W. Effect of ethanol on proliferation and estrogen receptor-α expression in human breast cancer cells. Cancer Lett 2001;165:131-137.
6. Dorgan JF, Baer DJ, Albert PS, et al. Serum hormones and the alcohol-breast cancer association in postmenopausal women. J Natl Cancer Inst 2001;93:710-715.
7. Enger S, Ross R, Paganini-Hill A, Longnecker M, Bernstein L. Alcohol consumption and breast cancer oestrogen and progesterone receptor status. Br J Cancer 1999;79:1308-1314.
8. Nasca P, Liu S, Baptiste M, Kwon S, Jacobson H, Metzger B. Alcohol consumption and breast cancer: estrogen receptor status and histology. Am J Epidemiol 1994;140:980-987.
9. Gapstur S, Potter J, Drinkard C, Folsom A. Synergistic effect between alcohol and estrogen replacement therapy on risk of breast cancer differs by estrogen progesterone receptor status in the Iowa Women's Health Study. Cancer Epidemiol Biomarkers Prev 1995;4:313-318.
10. Cooper J, Rohan T, Cant E, Horsfall D, Tilley W. Risk factors for breast cancer by oestrogen receptor status: a population-based case-control study. Br J Cancer 1989;59:119-125.
11. Yoo K, Tagima K, Miura S, et al. Breast cancer risk factors according to confined estrogen and progesterone receptor status: a case-control analysis. Am J Epidemiol 1997;146:307-314.

12. Stierer M, Rosen H, Weber R, Hanak H, Spona J, Tuchler H. Immunohistochemical and biochemical measurement of estrogen and progesterone receptors in primary breast cancer: Correlation of histopathology and prognostic factors. Ann Surg 1993;218:13-21.
13. Newcomer LM, Newcomb PA, Daling JR, Yasui Y, Potter JD. Post-menopausal hormone use and risk of breast cancer by histologic type. Am J Epidemiol 1999;149:S79.
14. Li CL, Weiss NS, Stanford JL, Daling JR. Hormone replacement therapy in relation to risk of lobular and ductal breast carcinoma in middle-aged women. Cancer 2000;88:2570-2577.
15. Chen CL, Weiss NS, Newcomb P, Barlow W, White E. Hormone replacement therapy in relation to breast cancer. JAMA 2002;287:734-741.
16. Newcomb PA, Titus-Ernstoff L, Egan KM, et al. Postmenopausal estrogen and progestin use in relation to breast cancer risk. Cancer Epidemiol Biomarker Prev 2002;11:593-600.
17. Daling JR, Malone KE, Doody DR, et al. Relation of Regimens of Combined Hormone Replacement Therapy to Lobular, Ductal, and Other Histologic Types of Breast Carcinoma. Cancer 2002;in press.
18. Breslow NE, Day NE. The Analysis of Case-Control Studies. Lyon, France: International Agency for Research on Cancer; 1980.
19. Begg CB, Gray R. Calculation of polychotomous logistic regression parameters using individualized regressions. Biometrika 1984;71:11-18.
20. Provisional table on the nutrient content of beverages. Washington, DC: Human Nutrition Information Service, US Department of Agriculture, 1982.
21. Smith-Warner SA, Spiegelman D, Yaun S-S, et al. Alcohol and breast cancer in women: a pooled analysis of cohort studies. JAMA 1998;279:535-540.
22. Zhang Y, Kreger BE, Dorgan JF, Splansky GL, Cupples LA, Ellison RC. Alcohol consumption and risk of breast cancer: The Framingham Study revisited. Am J Epidemiol 1999;149:93-101.
23. Giovannucci E, Stampfer MJ, Colditz GA, et al. Recall and selection bias in reporting past alcohol consumption among breast cancer cases. Cancer Causes Control 1993;4:441-448.

24. Hankinson SE, Willett WC, Manson JE, et al. Alcohol, height, and adiposity in relation to estrogen and prolactin levels in postmenopausal women. J Natl Cancer Inst 1995;87:1297-1302.

25. Ruder HJ, Loriaux L, Lipsett MB. Estrone sulfate: production rate and metabolism in man. J Clin Invest 1972;51:1020-1033.

BIBLIOGRAPHY

Acs G, Lawton TJ, Rebbeck TR, LiVolsi VA, Zhang PJ. Differential expression of E-cadherin in lobular and ductal neoplasms of the breast and its biologic and diagnostic implications. Am J Clin Pathol 2001;115:85-98.

Azzopardi GJ. Problems in Breast Pathology (1st ed). Eastbourne: WB Saunders, 1979; Chapter 11: 240-257.

Begg CB, Gray R. Calculation of polychotomous logistic regression parameters using individualized regressions. Biometrika 1984;71:11-18.

Bernstein L. The epidemiology of breast cancer. Women Cancer 1998;1S:7-13.

Breslow NE, Day NE. The Analysis of Case-Control Studies. Lyon, France: International Agency for Research on Cancer; 1980.

Chen CL, Weiss NS, Newcomb P, Barlow W, White E. Hormone replacement therapy in relation to breast cancer. JAMA 2002;287:734-741.

Colditz GA, Hankinson SE, Hunter DJ, et al. The use of estrogens and progestins and the risk of breast cancer in postmenopausal women. New Engl J Med 1995;332:1589-1593.

Colditz GA, Stampfer MJ, Willett WC, Hennekens CH, Rosner B, Speizer FE. Prospective study of estrogen replacement therapy and risk of breast cancer in postmenopausal women. JAMA 1990;264:2648-2653.

Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and hormonal contraceptives. Lancet 1996;347:1713-1727.

Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and hormone replacement therapy: collaborative reanalysis of data from 51 epidemiological studies of 52,705 women with breast cancer and 108,411 women without breast cancer. Lancet 1997;350:1047-1059.

Cooper J, Rohan T, Cant E, Horsfall D, Tilley W. Risk factors for breast cancer by oestrogen receptor status: a population-based case-control study. Br J Cancer 1989;59:119-125.

Daling JR, Malone KE, Doody DR, Johnson LG, Gralow JR, Porter PL. Relation of body mass index to tumor markers and survival among young women with invasive ductal breast carcinoma. Cancer 2001;92:720-729.

Daling JR, Malone KE, Doody DR, et al. Relation of Regimens of Combined Hormone Replacement Therapy to Lobular, Ductal, and Other Histologic Types of Breast Carcinoma. Cancer 2002;in press.

Dixon J, Anderson T, Page D, Lee D, Duffy S. Infiltrating lobular carcinoma of the breast. Histopathology 1982;6:149-161.

Dorgan JF, Baer DJ, Albert PS, et al. Serum hormones and the alcohol-breast cancer association in postmenopausal women. J Natl Cancer Inst 2001;93:710-715.

Du Toit RS, Locker AP, Ellis IO, et al. An evaluation of differences in prognosis, recurrence patterns and receptor status between invasive lobular and other invasive carcinomas of the breast. Eur J Surg Oncology 1991;17:251-257.

Ellison RC, Zhang Y, McLennan CE, Rothman KJ. Exploring the relation of alcohol consumption to risk of breast cancer. Am J Epidemiol 2001;154:740-747.

Enger S, Ross R, Paganini-Hill A, Longnecker M, Bernstein L. Alcohol consumption and breast cancer oestrogen and progesterone receptor status. Br J Cancer 1999;79:1308-1314.

Fan S, Meng Q, Gao B, Grossman J, Yadegari M, Goldberg ID, Rosen EM. Alcohol Stimulates Estrogen Receptor Signaling in Human Breast Cancer Cell Lines. Cancer Res 2000;60:5635-5639.

Gapstur S, Potter J, Drinkard C, Folsom A. Synergistic effect between alcohol and estrogen replacement therapy on risk of breast cancer differs by estrogen progesterone receptor status in the Iowa Women's Health Study. Cancer Epidemiol Biomarkers Prev 1995;4:313-318.

Giovannucci E, Stampfer MJ, Colditz GA, et al. Recall and selection bias in reporting past alcohol consumption among breast cancer cases. Cancer Causes Control 1993;4:441-448.

Goodman MT, Nomura AMY, Wilkins LR, Kolonel LN. Agreement between interview information and physician records on history of menopausal estrogen use. Am J Epidemiol 1990;131:815-825.

Hankinson SE, Willett WC, Manson JE, et al. Alcohol, height, and adiposity in relation to estrogen and prolactin levels in postmenopausal women. J Natl Cancer Inst 1995;87:1297-1302.

Jain MG, Rohan TE, Howe GR. Agreement of self-reported use of menopausal hormone replacement therapy with physician reports. Epidemiology 1999;10:260-263.

Lee AH, Dublin EA, Bobrow LG, Poulsom R. Invasive lobular and invasive ductal carcinoma of the breast show distinct patterns of vascular endothelial growth factor expression and angiogenesis. J Pathol 1998;185:394-401.

Li CI, Malone KE, Porter PL, Weiss NS, Daling JR. The relationship between long-term use of hormone replacement therapy and risk of breast cancer among women 65-79 years of age. Unpublished (see Chapter 1).

Li CL, Anderson BO, Porter P, Holt SK, Daling JR, Moe RE. Changing incidence rate of invasive lobular breast carcinoma among older women. Cancer 2000;88:2561-2569.

Li CL, Weiss NS, Stanford JL, Daling JR. Hormone replacement therapy in relation to risk of lobular and ductal breast carcinoma in middle-aged women. Cancer 2000;88:2570-2577.

Nasca P, Liu S, Baptiste M, Kwon S, Jacobson H, Metzger B. Alcohol consumption and breast cancer: estrogen receptor status and histology. Am J Epidemiol 1994;140:980-987.

Newcomb PA, Titus-Ernstoff L, Egan KM, et al. Postmenopausal estrogen and progestin use in relation to breast cancer risk. Cancer Epidemiol Biomarker Prev 2002;11:593-600.

Newcomer LM, Newcomb PA, Daling JR, Yasui Y, Potter JD. Post-menopausal hormone use and risk of breast cancer by histologic type. Am J Epidemiol 1999;149:S79.

Oyama T, Kashiwabara K, Yoshimoto K, Arnold A, Koerner F. Frequent overexpression of the cyclin D1 oncogene in invasive lobular carcinoma of the breast. Cancer Res 1998;58:2876-

2880.

Pagnini-Hill A, Ross RK. Reliability of recall of drug usage and other health-related information. Am J Epidemiol 1982;116:114-122.

Persson I, Bergkvist L, Adami H-O. Reliability of women's histories of climacteric oestrogen treatment assessed by prescription forms. Int J Epidemiol 1987;16:222-228.

Ross RK, Paganini-Hill A, Wan PC, Pike MC. Effect of hormone replacement therapy on breast cancer risk: estrogen versus estrogen plus progestin. J Natl Cancer Inst 2000;92:328-332.

Ruder HJ, Loriaux L, Lipsett MB. Estrone sulfate: production rate and metabolism in man. J Clin Invest 1972;51:1020-1033.

Singletary K, Frey R, Yan W. Effect of ethanol on proliferation and estrogen receptor-α expression in human breast cancer cells. Cancer Lett 2001;165:131-137.

Singletary KW, Gapstur SM. Alcohol and breast cancer: review of epidemiologic and experimental evidence and potential mechanisms. JAMA 2001;286:2143-151.

Smith-Warner SA, Spiegelman D, Yaun S-S, et al. Alcohol and breast cancer in women: a pooled analysis of cohort studies. JAMA 1998;279:535-540.

Stalsberg H, Thomas DB, Noonan EA, The WHO Collaborative Study of Neoplasia and Steroid Contraceptives. Histologic types of breast carcinoma in relation to international variation and breast cancer risk factors. Int J Cancer 1989; 44: 399-409.

Steinberg KK, Smith SJ, Thacker SB, Stroup DF. Breast cancer risk and duration of estrogen use: the role of study design in meta-analysis. Epidemiology 1994;5:415-421.

Stierer M, Rosen H, Weber R, Hanak H, Spona J, Tuchler H. Immunohistochemical and biochemical measurement of estrogen and progesterone receptors in primary breast cancer: Correlation of histopathology and prognostic factors. Ann Surg 1993;218:13-21.

Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. JAMA 2002;288:321-333.

Yoo K, Tagima K, Miura S, et al. Breast cancer risk factors according to confined estrogen and progesterone receptor status: a case-control analysis. Am J Epidemiol 1997;146:307-314.

Zhang Y, Kreger BE, Dorgan JF, Splansky GL, Cupples LA, Ellison RC. Alcohol consumption and risk of breast cancer: The Framingham Study revisited. Am J Epidemiol 1999;149:93-101.

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