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Hormonal and reproductive factors and risk of postmenopausal thyroid cancer in the NIH-AARP Diet and Health Study

SJ Schonfeld[1], **E Ron**[1,*], **CM Kitahara**[1], **A Brenner**[1], **Y Park**[1], **AJ Sigurdson**[1], **A Schatzkin**[1,*], and **A Berrington de González**[1]

[1]Division of Cancer Epidemiology and Genetics, National Cancer Institute, 6120 Executive Blvd, Bethesda, Maryland 20892, USA

Abstract

Background—Worldwide, thyroid cancer incidence rates are higher among women than men. While this suggests a possible etiologic role of female sex hormones, clear associations between hormonal and reproductive factors and thyroid cancer have not been observed. However, few large prospective studies have been conducted.

Methods—Hazard ratios (HRs) and 95% confidence intervals (CIs) for hormonal and reproductive factors and incident thyroid cancer were estimated using Cox regression methods in the prospective US NIH-AARP Diet and Health Study. Between 1995 and 2006, 312 first primary incident thyroid cancers were diagnosed among 187 865 postmenopausal women ages 50-71 at baseline.

Results—Thyroid cancer was not associated with ages at menarche or menopause, menopause type, or parity. Oral contraceptive use for ≥10 years (vs. never use) was inversely associated with thyroid cancer risk (HR, 0.48; 95%CI, 0.28-0.84; P_{trend}=0.01). Women who reported current menopausal hormone therapy at baseline had an increased thyroid cancer risk vs. never users (HR 1.38; 95% CI: 1.07-1.79) but there was no trend with increasing duration of use. Women with benign breast disease (BBD) had a significantly higher thyroid cancer risk vs. women without BBD (HR, 1.47; 95% CI, 1.09-1.99).

Conclusions—Our results do not support a strong role for female hormonal and reproductive factors including ages at menarche and menopause, type of menopause or parity, in thyroid cancer etiology among postmenopausal women. Compared with previous studies, no clear patterns emerge for exogenous hormone use but further analysis in large, prospective populations may be informative. The HR for BBD is consistent with the one previous prospective analysis that examined this association.

Keywords

thyroid/endocrine-related cancer; postmenopausal; reproductive; hormonal and related risk factors; benign breast disease

Corresponding author: Sara Schonfeld, Radiation Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, 6120 Executive Blvd., Bethesda, MD, 20892-7238, (schonfes@mail.nih.gov).
*Deceased

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Introduction

The incidence of thyroid cancer in the U.S. is increasing steadily [1] and there are few established risk factors beyond radiation and benign thyroid disease [2]. Higher thyroid cancer incidence rates among women compared with men worldwide [3] suggest a possible etiologic role of female sex hormones. In the U.S., the sex incidence rate ratio remains significantly above one until the eighth decade [4]. Additionally, thyroid gland volume increases during puberty [5] and sometimes during pregnancy [6] and fluctuates throughout the menstrual cycle [7]. Thyroid cancer cells express estrogen receptors and estradiol stimulates proliferation of papillary thyroid cancer cells in vitro [8].

Epidemiologic studies have not found consistent associations between hormonal and reproductive factors and thyroid cancer risk [2, 9-14]. These data are primarily based on case-control studies, including a large, pooled analysis of 14 case-control studies [11, 12, 15]. Few cohort studies [9, 10, 13, 14] have had sufficient numbers of thyroid cancers to prospectively analyze hormonal and reproductive risk factors, particularly among postmenopausal women. In the U.S., the largest increases in papillary thyroid cancer rates among women between 1980 and 2005 occurred among 60-79 year olds [16]. We evaluated whether hormonal and reproductive factors are associated with thyroid cancer risk among 187 865 postmenopausal women in the prospective US NIH-AARP (formerly known as the American Association of Retired Persons) Diet and Health Study (NIH-AARP).

Materials and methods

Study population

NIH-AARP [17] was established in 1995-1996 when 3.5 million AARP members ages 50-71 were mailed a self-administered questionnaire eliciting information on demographic and anthropometric characteristics, dietary intake, and numerous health-related behaviors. Participants were recruited from six U.S. states (California, Florida, Louisiana, New Jersey, North Carolina, and Pennsylvania) and two metropolitan areas (Atlanta, Georgia, and Detroit, Michigan). A second questionnaire was sent to participants in 1996-1997 seeking additional risk factor information.

From the baseline cohort of 226 732 women, we excluded women who used a proxy respondent (n=1265), women who completed a questionnaire but died or were diagnosed with any cancer other than non-melanoma skin cancer (NMSC) before the questionnaire was scanned (n = 23 935), as well as women who were premenopausal or had unknown menopausal status (n=9426). A woman was considered postmenopausal if she provided an age at last menstrual period, reported that her periods stopped due to natural menopause, surgery, radiation or chemotherapy, and did not have any conflicting data. Women who did not provide an age at last menstrual period but met the other two conditions were also classified as postmenopausal. Women who did not meet these criteria but were at least 57 and provided an age at last menstrual period or at least one reason for periods stopping or indicated use of postmenopausal hormones were also considered postmenopausal. Additionally, women ≤57 years who reported a bilateral oophorectomy or hysterectomy and either provided an age at last menstrual period or indicated that their periods had stopped were presumed to be postmenopausal as were women ≤57 years who indicated they were still menstruating but that their periods had stopped due to natural menopause and reported postmenopausal hormone therapy use. We further excluded women who reported at baseline that their periods had stopped due to radiation or chemotherapy or were missing information about cause of menopause (n=4241). The final baseline analytic sample consisted of 187 865 women; 119 257 women also completed the second questionnaire. The study was approved by the Special Studies Institutional Review Board of the National Cancer Institute.

Ascertainment of exposure and covariate information

At baseline, participants reported on ages at first (≤10, 11-12, 13-14, ≥15 years) and last menstrual period (<40, 40-44, 45-49, 50-54, ≥55, still menstruating), reason why periods stopped (periods did not stop, natural menopause, surgery, radiation or chemotherapy), parity (number of live births (none, 1, 2, 3-4, 5-9, ≥10) and age at first live birth (never gave birth, <16, 16-19, 20-24, 25-29, 30-34, 35-39, ≥40 years), oral contraceptive (OC) use (never or <1 year, 1-4, 5-9, ≥10 years), and menopausal hormone therapy (MHT) use (current use (yes, no), duration of use (never, <5, 5-9, ≥10 years)). There were also questions about hysterectomy and oophorectomy. Potential confounders of interest for the present study were also collected at baseline: race, education, current smoking status, height, weight, and typical alcohol consumption in the last year. The second questionnaire included a question about history of benign breast disease (BBD) which was associated with an increased risk of thyroid cancer in a recent cohort study [13]. Specifically, women were asked whether a doctor ever told them they had benign breast lumps or fibrocystic breast disease. The second questionnaire also asked about the type of MHT used (e.g., estrogen only vs. combined estrogen plus progestin).

Cohort follow-up and outcome ascertainment

Study participants are followed annually for change of address by matching the cohort database to that of the National Change of Address (NCOA) maintained by the U.S. Postal Service (USPS). Additionally, address change information is obtained from other sources including receipt of USPS processing of undeliverable mail, other address change update services, and communication from participants. Vital status is ascertained by annual linkage to the Social Security Administration Death Master File (SSA DMF) on deaths in the U.S., follow-up searches of the National Death Index (NDI) for subjects that match to the SSA DMF, cancer registry linkage, questionnaire responses, and responses to other mailings. The loss-to-follow-up rate in the study is approximately 5%.

First primary incident cases of thyroid cancer diagnosed between 1995 and 2006 were identified by probabilistic linkage between the study roster and ten state cancer registry databases estimated to be 90% complete within two years of cancer incidence and certified by the North American Association of Central Cancer Registries for meeting the highest standard of data quality. Total thyroid cancer (C73.9) was broken down by histologic type using the following International Classification of Diseases for Oncology, Third Edition morphology codes: papillary (8050, 8052, 8130, 8260, 8340, 8341, 8342, 8343, 8344, 8450, 8452); follicular (8290, 8330, 8331, 8332, 8335); medullary (8345, 8346, 8510); and anaplastic (8021) [18].

Statistical analysis

Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using multivariable Cox regression methods (Proc PHREG, SAS v. 9.1) with attained age as the underlying time metric. All covariates were modeled categorically with a separate category for missing data (≤1.5% for each of the hormonal and reproductive factors examined). Linear trend tests were conducted by modeling categorical values as ordinal variables using the original categories in which data were collected on the questionnaire. Some categories were combined in the tables to present more stable HR estimates. All models were adjusted for smoking status (never, former, current, unknown), race (white, other/unknown), education (less than college graduate, college graduate or higher, unknown), body mass index (kg/m^2) (calculated from height and weight) (<25, 25-<30, ≥30, unknown) and typical alcohol consumption (never, ever) in the last 12 months. Thyroid cancer was inversely associated with alcohol consumption [19] and positively associated with BMI [20] in previous NIH-AARP analyses. Hormonal and reproductive factors were mutually adjusted for each other;

each factor was also examined individually. The hazard plots confirmed assumptions of proportional hazards for all covariates.

For most analyses, follow-up began at age at the time the baseline questionnaire was scanned. Women were considered at risk until they experienced a first primary thyroid cancer diagnosis or were censored due to death, diagnosis of cancer other than thyroid cancer or NMSC, loss to follow-up, or December 31, 2006 (administrative censor), whichever occurred first. For the analyses of BBD and type of MHT use (none vs. estrogen only, none vs. combined estrogen and progestin), entry was defined as age at the scan date of the second questionnaire (when these exposures were ascertained). In addition to overall thyroid cancer analyses, we conducted analyses in which the outcome was defined as papillary cancer or follicular cancer, censoring participants at diagnosis of the non-event subtype of thyroid cancer.

Results

During a mean follow-up of 9.3 years, 312 women were diagnosed with a first primary thyroid cancer, including 229 papillary, 52 follicular, 12 medullary, and 9 anaplastic thyroid cancers. Histologic type was unknown for the remaining 10 cases. Basic cohort characteristics are described in Table 1. The distribution of hormonal and reproductive factors is presented in Table 2. The majority of women were parous (85%). Nearly 60% of women reported a natural menopause with most women reporting an age at natural menopause by age 55. Approximately 20% of women reported ≥5 years of OC use whereas slightly more than half of women reported use of MHT at some time. BBD was reported among 35% of women who completed the second questionnaire.

Thyroid cancer risk was not associated with age at menarche or menopause, type of menopause or parity (ever/never, age at first birth and number live births) (Table 2). The associations remained null when we examined age at menarche and number of births in finer categories than those shown in the table. We observed an inverse association between long-term OC use and thyroid cancer; compared with no or <1 year previous OC use, the HR for ≥10 years of OC use was 0.48 (95% CI, 0.28-0.84; P_{trend} = 0.01). Compared with women who reported no history of MHT use, former (HR, 1.28; 95% CI, 0.86-1.89) and current MHT users (HR, 1.38; 95% CI, 1.07-1.79) had an increased thyroid cancer risk but when these groups were further classified according to duration of use (<5 years and ≥5 years) there was no evidence of a trend with increasing duration of use among either former (P_{trend} =0.36) or current users (P_{trend} =0.20).

Within the subset of women who completed the second questionnaire, the adjusted HRs for ever use of MHT use compared with never use were 1.12 (95% CI, 0.74 – 1.71) for estrogen only MHT and 1.40 (95% CI, 0.96 – 2.04) for women who had ever used combined estrogen and progestin therapy.

Also based on the group of women who completed the second questionnaire, the risk of thyroid cancer was significantly higher among women who reported a diagnosis of BBD relative to those without BBD (HR, 1.47; 95% CI, 1.09-1.99). Recognizing that this observed risk could reflect increased surveillance among women with BBD, we conducted an analysis excluding the first 2 years of follow-up and the positive association persisted (HR, 1.39; 95% CI, 1.00-1.91).

Analyses of the associations between hormonal and reproductive factors by thyroid cancer subtypes did not suggest any substantial differences between papillary and follicular cancers, although small numbers of follicular thyroid cancers limited this comparison (data not shown).

Discussion

A possible hormonal etiology of thyroid cancer is hypothesized given the substantially higher incidence rates of this cancer among women compared with men [3] and the proliferative effect of estrogen on thyroid cells [8]. Previous epidemiologic studies have yielded inconsistent results regarding the role of hormonal and reproductive factors in the development of thyroid cancer, as shown in Table 3. The results from this large, prospective study of 312 thyroid cancer cases among 187 865 postmenopausal women do not support a strong role for the examined female hormonal and reproductive factors in the etiology of postmenopausal thyroid cancer.

The largest epidemiologic thyroid cancer study to date, a pooled analysis of 14 case-control studies conducted in Europe, Asia and North America, reported on many of the hormonal and reproductive factors also examined in the present study [11, 12]. The results of the pooled study, summarized previously [2, 21] were predominantly null or weak associations. Factors that were suggestive of an increased risk of thyroid cancer included older age at menarche, surgical menopause vs. premenopausal status, ever vs. never parous, and later age at first birth, and these were mainly observed among younger women in age-stratified analyses [11, 12]. These factors were not associated with thyroid cancer in the present study of postmenopausal women.

OC use was inversely associated with thyroid cancer in the present study. Women who reported ≥10 years of OC use had approximately one-half the risk of thyroid cancer compared with never users. In the pooled study, an inverse association between ever use of OCs and thyroid cancer was observed among women ≥56 and older at diagnosis (odds ratio (OR) =0.73), whereas there was a somewhat increased risk for women ≤35 years (OR=1.39) and no association among women 36-55 years at diagnosis (OR=1.04; p-interaction 0.05) [11]. Previous prospective studies have found no association between OC use and thyroid cancer risk [9, 13, 14]. Although analysis of time since last OC use in the pooled study suggested that the increased risk was restricted to current users [11] (who are more likely to be younger than former users), it is not clear why OCs would decrease the risk of thyroid cancer among older women. Formulation differences over calendar time [22] could play a role in the observed heterogeneity between older and younger women across the literature. The number of cases, and age range studied, did not allow analyses of results by age at entry in our cohort.

We observed a statistically significantly elevated risk of thyroid cancer among women who reported current MHT use at baseline but there was no clear trend with increasing duration of use. As the risk estimates for current short-term users (<5 years) were actually higher than for longer duration of use, our results may reflect increased surveillance among women who have recently started using MHT. High levels of estrogen increase thyroxine-binding globulin levels in women but their effect on thyroid-stimulating hormone, a suspected contributor to thyroid carcinogenesis [23], depends on thyroid function [24]. In euthyroid women, increased estrogen levels can lead to transient increases in TSH but normal levels are quickly reestablished whereas longer term TSH increases have been observed in women with hypothyroidism [24]. We did not have information about thyroid function and could therefore not examine whether the observed association differed by thyroid function status. The large, pooled case-control study and other previous epidemiologic studies have not found any indication that MHT use is a risk factor for thyroid cancer [9, 11, 13]. These studies did not distinguish between estrogen only and combined estrogen and progestin therapy. We had limited case numbers in which to do this, as evidenced by the wide confidence intervals, particularly for estrogen only use.

Within the subset of women who completed the second questionnaire, we observed a 1.47-fold increased risk of thyroid cancer among women with BBD compared with women who reported no previous diagnosis of BBD. This was very consistent with the HR (1.56) reported in a large prospective study of U.S. radiologic technologists [13]. This finding may reflect greater surveillance of women with BBD. There may also be shared risk factors in breast and thyroid disease that we could not account for in this study, as suggested by the increased risk of a second primary thyroid and breast cancers after diagnosis of the other [25]. Several studies have reported an association between thyroid dysfunction and breast disease, benign and malignant [26, 27]. We did not have information about the type of benign breast disease or the date of diagnosis. Benign breast disease encompasses a heterogeneous group of conditions and the magnitude of breast cancer risk varies across BBD type [28]. A more detailed investigation of thyroid cancer risk according to different subtypes of benign breast disease and age at diagnosis is needed to better understand our result and previously observed associations between thyroid and breast diseases.

A limitation of this study was the lack of tumor size information. Many small papillary thyroid cancers are thought to be incidental findings [29]. A comparison of the associations with BBD by tumor size could indicate the likelihood that increased surveillance accounts for this association. Also, small numbers of non-papillary thyroid cancers limited comparisons by histologic type. Nonetheless, prospective evaluation of hormonal and reproductive factors in a large sample of postmenopausal women including over 300 thyroid cases uniquely enabled a detailed investigation of factors specific to postmenopausal women (e.g., MHT use and factors related to menopause), as well as premenopausal exposures.

Overall, the results from this large prospective study do not support a strong role for female hormonal and reproductive factors including ages at menarche and menopause, type of menopause or parity (age at first birth or number of live births), in thyroid cancer etiology among postmenopausal women. Compared with previous studies, no clear patterns emerge for exogenous hormone use. Further analysis of OC use and MHT use in large, prospective studies may be informative, particularly in those with information about MHT formulation. The observed increased risk among women with BBD is consistent with the one previous prospective analysis that examined this association and future investigations may be warranted to better understand the observed associations between breast and thyroid pathologies.

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Table 1

Select baseline characteristics of 187,865 postmenopausal women in the NIH-AARP Diet and Health Study

	No. Women	% of Women	No. Cases
All women	187 865		312
Mean age (years) at entry (range)	62.2 (50.3 - 71.5)		
Mean years of follow-up	9.3 (0.01 – 11.2)		
Race			
Non-hispanic white	167 694	89.3%	283
Non-hispanic black	10 896	5.8%	16
Hispanic	3609	1.9%	4
Asian /Pacific Islander/American Indian/Alaskan native	2950	1.6%	4
Unknown	2716	1.5%	5
Smoking status			
Never	82 781	44.1%	148
Former	72 209	38.4%	125
Current	27 285	14.5%	26
Unknown	5590	3.0%	13
Body mass index			
<25 kg/m^2	79 839	42.5%	113
25- <30 kg/m^2	59 412	31.6%	105
≥30 kg/m^2	42 622	22.7%	84
Unknown	5992	3.2%	10
Education			
Less than college graduate	127 238	67.7%	209
College graduate or graduate degree	54 502	29.0%	88
Unknown	6125	3.3%	15
Consumption of alcoholic drinks			
Never drink	56 535	30.1%	114
Ever drink	131 330	69.9%	198
Unknown	0	0	0

Table 2

Hormonal and reproductive factors and risk of thyroid cancer among 187 865 postmenopausal women in the NIH-AARP Diet and Health Study

	No. Women	No. cases	HRs[a]	95% CIs	P- trend[b]
Age at menarche					
<13 years	91 762 (48.8)	158	1.00	Reference	
≥13 years	95 556 (50.9)	153	0.94	(0.75 - 1.18)	*0.40*
Parity					
Nulliparous	26 295 (14.0)	40	0.97	(0.69 - 1.36)	
Parous	160 211 (85.3)	270	1.00	Reference	
Number of live births among parous women					
1-2	67 441 (42.1)	123	1.00	Reference	
≥3	91 771 (57.3)	143	0.81	(0.63 - 1.04)	*0.29*
Age at first birth among parous women					
<20 years	33 702 (21.0)	41	0.67	(0.47-0.95)	
20-24 years	82 188 (51.3)	151	1.00	Reference	
25-29 years	32 994 (20.6)	58	0.93	(0.68 - 1.27)	
≥30 years	10 798 (6.7)	19	0.88	(0.54 - 1.44)	*0.37*
Type of menopause					
Natural	110 909 (59.0)	165	1.00	Reference	
Surgical	76 956 (41.0)	147	1.22	(0.93 - 1.61)	
Age at natural menopause[c]					
<50 years	44 626 (40.2)	58	0.90	(0.64 - 1.26)	
50-54 years	53 495 (48.2)	81	1.00	Reference	
≥55 years	11 983 (10.8)	25	1.29	(0.82 - 2.03)	*0.26*
Age at surgical menopause[d]					
<45 years	51 525 (67.0)	93	1.00	Reference	
45-49 years	16 204 (21.1)	36	1.26	(0.85 - 1.85)	
≥50 years	8711 (11.3)	17	1.05	(0.62 - 1.76)	*0.61*
Oral contraceptive use					
Never/<1 year	114 552 (61.0)	203	1.00	Reference	
1 - <5 years	32 089 (17.1)	66	1.23	(0.93 - 1.65)	

	No. Women	No. cases	HRs[a]	95% CIs	P- trend[b]
5-9 years	22 534 (12.0)	26	0.70	(0.46 - 1.06)	
≥ 10 years	17 269 (9.2)	14	0.48	(0.28 - 0.84)	*0.01*
Menopausal hormone therapy use					
Never	87 499 (46.6)	124	1.00	Reference	
Former[e]	17 666 (9.4)	33	1.28	(0.86 - 1.89)	
Former, <5 years	12 933 (6.9)	24	1.26	(0.81 - 1.96)	
Former, ≥ 5 years	4619 (2.5)	9	1.30	(0.66 - 2.57)	*0.36*[f]
Current[e]	82 273 (43.8)	154	1.38	(1.07 - 1.79)	
Current, <5 years	22 758 (12.1)	47	1.63	(1.15 - 2.31)	
Current, ≥ 5 years	59 480 (31.7)	107	1.28	(0.96 - 1.71)	*0.20*[g]
Benign breast disease[h]					
No	76 053 (63.4)	99	1.00	Reference	
Yes	41 709 (35.0)	81	1.47	(1.09 - 1.99)	

[a] Hazard ratios (HRs) and 95% confidence intervals (95% CIs) estimated from Cox proportional hazards models (SAS v9.1, PHREG) that used attained age as the time metric. Mutually adjusted models include the following hormonal/reproductive variables (as categorized in the table): age at menarche, ever parous, oral contraceptive use duration, menopausal hormone therapy use (defined by status and duration of use), menopause type, and age at last menstrual period (<50, 50-54, ≥55), unless otherwise specified. Models further adjusted for smoking status, baseline BMI, race, alcohol consumption, and education. Models restricted to parous women mutually adjusted for age at first birth and number of births.

[b] Linear trend tests were conducted by modeling categorical values as ordinal variables using the original categories in which data were collected on the questionnaire.

[c] Restricted to women reporting a natural menopause.

[d] Restricted to women reporting a surgical menopause.

[e] Totals include women with unknown duration of use.

[f] Trend test for duration among former MHT users.

[g] Trend test for duration among current MHT users.

[h] Among women who completed the second questionnaire.

Table 3

Comparison of overall associations between thyroid cancer and hormonal and reproductive factors across studies

	Pooled Case-Control	Summary of cohort studies with ≥100 thyroid cancers				Present study
Factor	**Negri et al. [12] La Vecchia et al. [11]**	**Akslen et al. [10]**	**Iribarren et al. [14]**	**Navarro Silvera et al. [9]**	**Meinhold et al. [13]**	**NIH-AARP**
	ORs[a] (95% CIs)	**R[b] (95% CIs)**	**HRs[c] (95% CIs)**	**HRs[c] (95% CIs)**	**HRs[c] (95% CIs)**	**HRs[c,d] (95% CIs)**
Number of cases Mean age at baseline (range)	2132 [11] / 2247 [12] NA (15-88) [15]	124 NA (32 - 74)	123 38.9 (10 - 89)	169 48 (40 - 59)	242 39.3 (NA)	312 62.2 (50.3 - 71.5)
Age (y) at menarche	*≥15 vs. <13:* 1.2 (1.0 - 1.4)	*≥ 15 vs. ≥13:* 0.9 (0.6 - 1.5)	*≥ 15 vs.13-14:* 0.8 (0. 4 - 1.5)	*≥12 vs. <12:* 1.0 (0.8 - 1.4)	*≥ 16 vs. <12:* 1.5 (0.7 - 2.9)	*≥13 vs. <13:* 0.9 (0.8 - 1.2)
Parous	*ever vs. never:* 1.2 (1.0 - 1.4)	*ever vs. never:* 1.0 (0.6 - 1.5)	-----	*ever vs. never:* 0.8 (0.4 - 1.3)	-----	*never vs. ever:* 1.0 (0.7 - 1.4)
Age (y) at menopause, adjusted for type	*≥ 53 vs. <45:* 0.8 (0.5 - 1.2)	*≥ 52 vs. ≥ 47:* 1.0 (0.4 - 2.3)	-----	-----	-----	*≥55 vs50-54:* 1.2 (0.8 - 1.8)
Oral contraceptive use (ever vs. never)	1.2 (1.0 - 1.4)	-----	1.1 (0.7 - 1.7)	1.1 (0.8 - 1.5)	1.3 (0.9 - 1.8)	0.9 (0.7 - 1.1)[e]
Menopausal hormone therapy use (ever vs. never)	0.8 (0.6 - 1.1)	-----	0.8 (0.5 - 1.4)	1.2 (0.7 - 2.0)	1.2 (0.6 - 2.2)	1.4 (1.1 - 1.7)[f]
Benign Breast Disease (yes vs. no)	-----	-----	-----	-----	1.6 (1.1 - 2.3)	1.5 (1.1 - 2.0)

[a] ORs, Odds Ratios; 95% CIs, Confidence Intervals;

[b] Rs, Relative Odds,

[c] HRs, Hazard Ratios

[d] Hormonal and reproductive factors mutually adjusted using models described for Table 2 unless otherwise specified. Models further adjusted for smoking status, baseline BMI, race, alcohol consumption, and education.

[e] Ever use of oral contraceptives substituted for duration of use.

[f] Ever use of menopausal hormone therapy substituted for use defined by duration and baseline status.