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Reproductive Cancer Risk Factors among Alaska Native Women: The Alaska Education and Research Towards Health (EARTH) Study

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Abstract

Background—The purpose of this study was to provide estimates for the prevalence of reproductive cancer risk factors among Alaska Native (AN) women who enrolled in the Alaska Education and Research Towards Health (EARTH) Study from 2004 to 2006.

Methods—A total of 2,315 AN women 18 years or older completed reproductive health questions as part of a comprehensive health history questionnaire. The reproductive health section included menstrual status (age at menarche and menopause), pregnancy and live birth history, use of hormonal contraception, hormone replacement therapy, and history of hysterectomy and/or oophorectomy.

Results—A total of 463 (20%) of women experienced menarche before age 12 with a decline in mean age at menarche by age cohort. More than 86% had been pregnant (mean number of pregnancies, 3.8; mean number of live births, 2.9). More than one half of women (58%) had their first live birth between the ages of 18 and 24. Almost 28% of participants had completed menopause, of whom 24% completed menopause after age 52. Fewer than half (43%) reported ever using hormone replacement therapy. Almost two thirds (62%) reported ever using oral contraceptives, and fewer reported ever using birth control shots (30%) or implants (10%).

Conclusions—This study is unique in reporting reproductive health factors among a large group of AN women. These data show that AN women have selective protective factors for reproductive cancers, including low nulliparity rates, low use of menopausal estrogens, and common use of contraceptive hormones. However, analysis by age cohorts indicates decreasing age at menarche that might increase the risk for reproductive cancers among AN women in the future.

Introduction

Cancer is the leading cause of death among Alaska Native (AN) women, despite being considered a rare disease in AN people as recently as the mid-twentieth century (Day, Provost, & Lanier, 2009; Lanier, 2006; U.S. Department of Health and Human Services, Indian Health Service, Office of Public Health Support, & Division of Program Statistics,

2008). From 1973 to 2003, AN women experienced 2,977 invasive cancers, of which 37% were at reproductive sites: breast, uterus, ovary, and cervix (Day, Lanier, Bulkow, Kelly, & Murphy, 2010). Data from 1999 to 2003 show that breast and cervical cancer incidence rates among AN women were similar to U.S. White rates, whereas rates for cancer of the uterus and ovary were significantly lower than those for U.S. Whites (Kelly, Day, Lanier, & Murphy, 2007). From 2004 to 2008, ovarian cancer incidence rates rose and are now similar to those of U.S. Whites (Surveillance, Epidemiology, and End Results Alaska Native Tumor Registry, personal communication, 2012).

The timing of menarche, menopause, and other reproductive events in a woman's life have been associated with a variety of health outcomes including reproductive cancers (Buchanan, Weinstein, & Hillson, 2009; Ebell, 2009; Medina, 2005; Steiner, Klubert, & Knutson, 2008), cardiovascular disease (Merz et al., 2009), and obesity (Lovejoy, 1998). Risk factors for reproductive cancers include use of menopausal estrogens, nulliparity, late age at natural menopause (>52 years), early age at menarche (<12 years), and long-term use of high-dose combination oral contraceptives (Buchanan et al., 2009; Ebell, 2009; Steiner et al., 2008). It is well established that age at menarche, parity, age at first birth, and other related factors vary across racial groups (Chen & Morgan, 1991; Henderson, Bernstein, Henderson, Kolonel, & Pike, 2008; Luborsky, Meyer, Sowers, Gold, & Santoro, 2002). However, most of the large, multiethnic studies, such as the Study of Women's Health Across the Nation (Sowers et al., 2000) or the Multi-Ethnic Cohort Study (Henderson et al., 2008), did not include either American Indian (AI) or AN (AI/AN) women. In general, data on the reproductive history of AI/AN women come from studies where a small number of the women were AI/AN and are limited to AI/AN women living outside of Alaska.

To date, no information exists on multiple reproductive cancer risk factors among AI/AN women living in Alaska. The Alaska Education and Research Towards Health (EARTH) study is a prospective cohort study of predominately AN people (95% AN, 5% AI) who reside in the state. We report baseline data collected at study enrollment (2004–2006) for age at menarche and menopause, parity and age at first birth, use of birth control and hormone replacement therapy, and prevalence of hysterectomy and/or oophorectomy. We compare the rates of these self-reported reproductive cancer risk factors with the limited data that exist in other surveys.

Materials and Methods

Study Population

The study population, data collection methods, and measurement instruments for the EARTH Study were described in detail by Slattery and colleagues (2007). Briefly, we recruited participants from 26 Alaskan communities in three regions of the state (Table 1). The south central Alaska region included AN people from many different ethnic groups living in or around Alaska's largest city with a total population of 350,000. The southeast Alaska region included mostly Tlingit, Haida, and Tsimshian Indian people living in smaller communities (ranging in population from 500 to 30,000). The southwest Alaska region included mostly Yupik people and was the most rural and remote of the three Alaskan regions, with communities ranging in population size from 200 to 5,500. All of the southeast and southwest Alaskan communities were located off the road system and were accessible only by airplane, with seasonal access by snow machine or boat.

Methods of recruitment for all regions included presentations to tribal groups and healthcare providers, information tables staffed by study personnel at community events, house-to-house recruiting, brochures and flyers in public locations, and public service announcements on local radio and in newspapers. In each community, we attempted to enroll all residents of

the community who met the following inclusion criteria: AN or AI eligible for care in the Alaska Tribal Health System, age 18 years of age or older, and able to provide written, informed consent. We asked pregnant women and chemotherapy patients to participate at a later date owing to health measurement changes caused by these two factors. Data presented come from 2,315 women enrolled in the study from March 2004 through August 2006. All eligible women in each participating community were invited to enroll in the study. Although not a random sample, the age distributions were similar to the 2000 census data from which the populations were derived (Slattery et al., 2007a,b). Compared with 2000 census data for each community, participation ranged from 2% to 49% of eligible adults age 18 and older, with a median of 29%.

Data Collection

EARTH participants completed interviewer-administered questionnaires on demographics, and self-administered questionnaires on diet, physical activity, lifestyle and cultural practices, environmental exposures, cancer screening practices, personal medical and reproductive history, and family history of chronic diseases. Participants completed the questionnaires by using computer-assisted self-interview on touch-screen panels while listening to an audio version of the questionnaire by headphones in English or Yupik (Edwards et al., 2007). The EARTH study pregnancy and reproductive health history section questions were adapted from the 4-Corners Breast Cancer Study (Slattery et al., 2007a,b; Sweeney et al., 2008) and included questions about age at menarche and menopause, pregnancy and live birth history, use of hormonal contraception, use of hormone replacement therapy, and history of hysterectomy and oophorectomy. Height, weight, waist and hip circumference, blood pressure, fasting glucose, and a lipid panel were also measured.

The study protocol was approved by the Alaska Area Institutional Review Board, the research and ethics committees and governing boards of each of the participating regional tribal health corporations, and the tribal councils of each participating community. All participants gave written informed consent before study participation.

Statistical Analysis

Descriptive statistics provide an overview of the demographic characteristics of participants. To evaluate the representativeness of the sample, comparisons were made with U.S. Census 2000 data for AN women residing in Alaska (U.S. Census Bureau, 2000). Data from participants who answered “don’t know/not sure” or who did not answer the question were excluded from the analyses (range, 1%–5%). Women in the Alaska EARTH Study were divided into age cohorts with age determined at the time of enrollment: 18 to 24, 25 to 44, 45 to 59, and 60 years or older to examine age cohort trends in reproductive characteristics using the chi-square test. We conducted all analyses using SPSS (version 16.0; SPSS, Inc., Chicago, IL) for Windows. The significance level was set at $p < .05$.

Results

Women ($n = 2,315$) in the Alaska EARTH Study ranged from age 18 to early 90s (mean, 41) at the time of recruitment (Table 1). The majority of participants (79%) completed high school or higher education and about half (48%) were currently employed. Compared with U.S. Census data for AI/AN women living in Alaska, women in the Alaska EARTH Study were more likely to be married or living as married, more likely to have a high school degree or higher, more likely to have household income under \$15,000 per annum, and less likely to report their health status as excellent/very good/good. Compared with U.S. Census

data for Alaska, a similar percentage of women in the Alaska EARTH Study spoke their AI/AN language at home. A total of 7% reported speaking only their native language at home.

The majority (69%) of women in the Alaska EARTH Study reported their age at menarche to be between 12 and 14 years, with a mean menarche age of 12.6 (Table 2). One fifth (20%) reported menarche before age 12. The age at menarche declined significantly by age cohort: Among women 18 to 24 years old, 26% reported their first menstrual period before age 12, compared with 15% of women 60 years or older (p for trend < .05). A total of 86% of participants had been pregnant in their lifetime, and the mean number of pregnancies was 3.8 (maximum, 17). A total of 38% reported 1 to 3 pregnancies, 43% reported 4 to 9 pregnancies, and 5% reported 10 or more pregnancies. The mean number of live births was 2.9 (maximum, 16). Almost half (46%) reported 1 to 3 live births, 33% reported 4 to 9 live births, and 2% reported 10 or more live births. Women in the older age cohorts (45–59 and 60) were more likely to report having 4 or more births (p for trend < .05). Most women had their first live birth at age 18 to 24 (58%), with 27% having their first live birth before age 18 and 14% having their first live birth between ages 25 and 34. Over half of women (58%) had experienced one or more miscarriages (mean, 1.0), with 5% experiencing 4 or more miscarriages. A total of 618 (28%) of the women reported that they had completed menopause, that is, their periods had stopped completely. Of those, a total of 140 (24%) completed menopause after age 52. Among women who did not have a hysterectomy, the mean age at menopause was 48 years. Of the women whose periods had stopped completely, 207 (34%) were because they had had a hysterectomy. A total of 231 women (10%) had had an oophorectomy. Of those who had a hysterectomy, 68% also had their ovaries removed (data not shown).

A total of 369 women (43%) reported using hormone replacement therapy either currently or at some point in the past, with over half (62%) using hormone replacement therapy for 4 years or less (Table 3). Almost two thirds of women in the study (62%) reported having taken birth control pills, with 236 (10%) reporting current use of birth control pills. Similar to hormone replacement therapy, about two thirds of women (69%) had taken birth control pills for 4 years or less. Only 134 (10%) of women reported taking birth control pills for 11 years or longer. Fewer women reported ever using birth control shots (30%) or birth control implants (10%).

Discussion

The Alaska EARTH Study is the largest exploration of reproductive health factors among AN women to date. The EARTH data suggest a younger age of menarche, age at first birth, and menopause compared with national and historic data (Matthews & Hamilton, 2002). In addition, the data suggest lower use of oral contraceptive agents and large family size. These data show that AN women have many protective factors for reproductive cancers, including low nulliparity rates, low use of menopausal estrogens, and some use of contraceptive hormones. However, the decline in age at menarche might increase the risk for reproductive cancers among AN women in the future. The EARTH data offers a unique insight into the use of long-term contraceptive agents that is not reported in similar female reproductive cross-sectional data.

EARTH data suggest that AN women report a younger age of menarche, age at first birth, and age of menopause than women in many other ethnic and racial groups (Dratva et al., 2009; Dratva et al., 2007; Henderson et al., 2008; Lawlor, Ebrahim, & Smith, 2003; Santoro et al., 2007). However, comparison with the Multiethnic Cohort Study, the British Women's Heart and Health Study, the Study of Women's Health Across the Nation, the Swiss Air Pollution and Lung Disease in Adults study, and other cross-sectional studies of

reproductive factors in non-North American Native women is difficult owing to varying methodologies.

Risk factors for reproductive cancers including early age at menarche (<12 years) and late age at natural menopause (>52 years) are well documented (Buchanan et al., 2009; Steiner et al., 2008). For example, a large international case-control study involving 3,993 breast cancer cases and 11,783 controls from 7 countries found that a 2-year delay in menarche corresponded with a 10% reduction in breast cancer risk (95% confidence interval [CI] 6%–15%). The same study also found that later age at menopause and larger body mass increased breast cancer risk with each 5-year increase in age at menopause, corresponding with a 17% increase in breast cancer risk (95% CI, 11%–22%) and each increase of 4 kg/m² corresponding to a 10% increase (95% CI, 6%–14%). Hsieh, Trichopoulos, Katsouyanni, & Yuasa (1990) found an interaction between age at menarche and obesity ($p = .04$), which suggests that the protective effect of a late age at menarche does not apply to obese women. This study did not include AN women. AN women are also not represented in the Multiethnic Cohort Study or in Study of Women's Health Across the Nation. In our study, the mean age of menarche was 12.6 years, and one quarter of study participants (24%) reported menopause after age 52. In comparison, the 1999 to 2002 NHANES II study revealed a mean age of menarche of 12.3 years in the United States for all races (Anderson & Must, 2005).

The most recent published data on AN menarche patterns antedate the Alaska EARTH study by 40 years. A 1968 demographic study of 139 females in northwest Alaska recorded a mean menarche age of 13.8 years (Milan, 1970a, 1970b). A 1930 survey of 32 southwest Alaska school girls noted a mean age of menarche of 13.3 years (Hrdlicka, 1936). A 1948 study of 122 females in another northwest Alaskan community reported a mean menarche age of 14.4 years (Levine, 1953). Data from the Alaska Pregnancy Risk Assessment Monitoring System (PRAMS) show a similar mean age at menarche among AN women who delivered a live-born infant from 2000 to 2003 (12.6 years) as the Alaska EARTH Study found among all female study participants from 2004 to 2006 (12.7 years; K. Perham-Hester, Alaska PRAMS Coordinator, State of Alaska, DHSS, Division of Public Health, personal communication, March 2012).

In 1932, Weyer reported the age of menarche in a variety of arctic and nonarctic Native peoples while noting the commonly held theory that a colder climate was associated with a later menarche versus earlier menarche in warmer climes. The Alaskan Eskimo average menarche was reported to be 14.2 years, whereas the more southern Native women had an average of 13.3 years. However, later data showed that if there was a climatic effect, it was quite small and often related to the nutrition status of the group (Tanner, 1978).

Alaska EARTH Study data are consistent with data from NHANES showing that the age of menarche continues to decline as female adolescent relative weight increases (Anderson & Must, 2005; McDowell, Brody, & Hughes, 2007). The nutrition theory has now been borne out by years of observation, namely that menarche is an indicator of lifestyle (Tanner, 1978). Despite examining several nutrient groups, it seems that no one particular energy source was associated with menarche; rather, there is an association with the overall accumulation of adipose tissue (Biro et al., 2001; Maclure, Travis, Willett, & MacMahon, 1991; Tanner, 1978; Zacharias & Wurtman, 1969).

The age of the mother, both younger and older, plays a strong role in a wide variety of birth outcomes, for example, birth weight, multiple births, and birth defects. In addition, the younger a woman is at her first full-term pregnancy, the lower her breast cancer risk (Rosner, Colditz, & Willett, 1994). The present data are consistent with the literature in

finding younger age at first birth among AN and AI people despite an increase in age at first birth across birth cohorts. Historical data for AN age at first birth was 18.0 years in 1968 in northwest Alaska (Milan, 1970a). This is similar to earlier findings across the circumpolar arctic north from the 1870s to the 1920s (Weyer, 1932). The Alaska EARTH study found a mean age at first birth of 20.9 years, younger than 2000 data from the United States (24.9 years) and Alaska, all races (24.3 years; Matthews & Hamilton, 2002), but older than the mean age from Alaska PRAMS data on AN women from 2000 to 2003 (19.4 years). It should be noted, however, that because of the nature of the question's wording, the self-reported age given for this particular PRAMS measure could have been interpreted as age at first conception, regardless of whether a live birth resulted from the pregnancy (K. Perham-Hester, Alaska PRAMS Coordinator, State of Alaska, DHSS, Division of Public Health, personal communication, March 2012). A review of U.S. National Vital Statistics data from 1970 to 2000 showed a steady increase in age at first live birth, from 21.4 years to 24.9 (an increase of 3.5 years). Likewise, Alaska statewide, all races, increased by 2.5 years from 21.6 to 24.1 over the same period. The U.S. National Vital Statistics trend has continued through 2006 with the national average age at first birth increasing to 25.0 and the state of Alaska, all races, to 24.3 years (Matthews & Hamilton, 2009).

Late age at natural menopause (>52 years) is a risk factor for reproductive cancers. The historically reported age at menopause in AN women was 44.5 years in 1968 in northwest Alaska (Milan, 1970b). The Alaska EARTH Study found that 28% of study participants had completed menopause, and 24% reported menopause after age 52. There was a mean menopause age of 45.6 years for the whole sample, which is younger than other published reports for AI women. The Strong Heart Study found a mean age of natural menopause of 46.8 years (Cowan et al., 1997), whereas Montana Blackfeet women reported 51.2 years (Johnston, 2001).

The strengths of this study are the size of the cohort and geographical diversity owing to inclusion of three different regions of Alaska with multiple AN ethnic groups represented. A further strength of the study is data on age of menarche and menopause, which have not been previously published from other data sources. A limitation of this study is the nonrandom sampling design and the inability to assess the relative contributions of these risk factors to incident reproductive cancers among AN women, specifically. Although the cohort was not randomly selected, the distribution of the study population closely resembled the demographic distributions reported by the 2000 U.S. Census for AI/AN in the respective regions (U.S. Census Bureau, 2000). All data were collected by self-report, potentially contributing to measurement error. Last, data reported here are cross-sectional from the initial study visit, and do not allow evaluation of causal relationships between variables. Further study is needed to understand whether the strength of the risk and protective factors for reproductive cancers among AN women is similar to that among other race and ethnic groups.

Conclusions

These data show that AN women have competing positive and negative risk factors for reproductive cancers. These findings support continued surveillance regarding female reproductive health practices, including pregnancies and births, onset of menses and menopause, and hormonal contraception and treatment for menopause and other disorders as they may relate to changing prevalence of cancer in women. In addition, these data support ongoing efforts to meet female cancer screening goals. The many protective factors for reproductive cancers identified in this study include low nulliparity rates, low use of menopausal estrogens, and use of contraceptive hormones. However, the Alaska EARTH has also documented a high obesity rate, high tobacco use, and low rates of physical activity

and healthy traditional food use in this population (Redwood et al., 2009; Redwood et al., 2008; Schumacher et al., 2008; Slattery et al., 2010; Smith, Ferucci, Dillard, & Lanier) These additional cancer risk factors may undermine the beneficial reproductive practices among this cohort. Additionally, changing reproductive health characteristics, including the decreasing age at menarche by age cohort, might increase the risk for reproductive cancers among AN women in the future. Further research is needed to monitor trends and understand the contribution of these competing risk factors to the incidence of reproductive cancers of AN women.

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Table 1

Characteristics of Alaska Native Women Participants of the EARTH Study, 2004 to 2006, Compared with Alaska Native Women, U.S. Census, 2000

Characteristic	EARTH Study, <i>n</i> (%; 95% CI)	Census, [*] <i>n</i> (%)
Total	2315 (100)	59,119 (100)
Region [†]		
Southcentral	933 (40; 38–43)	19,056 (27)
Southeast	557 (24; 22–26)	7,578 (52)
Southwest	825 (36; 33–38)	4,707 (21)
Age (yrs) [‡]		
18–39	1130 (49; 46–52)	18,534 (51)
40–51	648 (28; 26–30)	9,302 (26)
52	537 (23; 21–25)	8,219 (23)
Marital status [§]		
Married/living as married	1112 (48; 45–51)	15,387 (39)
Separated/divorced/never married/widowed	1193 (52; 49–55)	24,466 (61)
Education [‡]		
High school diploma or more	1815 (79; 75–83)	26,512 (74)
Employment status (women only) [¶]		
Employed or self-employed	1119 (48; 45–51)	19,109 (50)
Annual household income, \$ (women and men) ^{//}		
<15,000	719 (36; 34–39)	6,536 (20)
15,000–24,999	309 (16; 14–17)	5,178 (16)
25,000–34,999	310 (16; 14–17)	4,403 (14)
35,000–49,999	296 (15; 13–17)	5,074 (16)
50,000	354 (17; 16–20)	10,904 (34)
Language spoken at home (women and men) [#]		
Non-English or both	715 (31; 29–33)	31,130 (29)
English only	1590 (69; 66–72)	76,435 (71)
Self-reported health status ^{**}		
Excellent, very good, or good	1721 (74; 71–78)	476 (80)
Fair or poor	593 (26; 24–28)	120 (20)

Abbreviations: AI/AN, American Indian/Alaska Native people; EARTH, Education and Research Towards Health.

^{*} Census 2000 data for Alaska Summary File 4 (U.S. Census Bureau, 2000). Totals do not equal 59,119 for all categories because of missing responses.

[†] Census 2000 data for the corresponding Alaska Native Regional Corporations [ANRC]) Southcentral: Cook Inlet ANRC; Southeast: Sealaska ANRC; Southwest: Calista ANRC.

[‡] Census 2000 data for population aged 18 (U.S. Census Bureau, 2000).

[§] Census 2000 data for population aged 15 years (U.S. Census Bureau, 2000).

[¶] Census 2000 data for population aged 16 years (U.S. Census Bureau, 2000).

// Census 2000 data for households. EARTH data were missing 555 responses for this variable (U.S. Census Bureau, 2000).

Census 2000 data for population aged 5 years (U.S. Census Bureau, 2000).

** Behavioral Risk Factor Surveillance System 2005, Alaska, Alaska Native women (Alaska Department of Health and Social Services, 2005).

Table 2

Reproductive Health Characteristics of Alaska Native Women, Alaska EARTH Study, 2004 to 2006

Variable	N	%
Age at menarche, yrs (mean, 12.6; 95% CI, 12.5–12.7)		
<12	463	20.3
12–14	1570	68.8
15–19	245	10.7
20	5	0.2
Age cohort at menarche (YES, <12 yrs)		
18–24	100	26.3
25–44	229	22.0
45–59	95	16.0
60	39	14.5
Ever been pregnant	1982	86.3
Number of pregnancies (mean, 3.8; 95% CI, 3.6–3.9)		
None	314	13.8
1–3	872	38.4
4–9	974	42.9
10	109	4.8
Maximum	17	
Number of live births (mean, 2.9; 95% CI, 2.8–3.0)		
Nulliparous	427	18.6
1–3	1062	46.3
4–9	766	33.4
10	37	1.6
Maximum	16	
Age at first live birth, yrs (mean, 20.9; 95% CI, 20.7–21.1)		
13–17	577	27.4
18–24	1210	57.5
25–34	296	14.1
35	22	1.0
Age cohort for first live birth (YES, <18 yrs)		
18–24	51	31.3
25–44	158	17.7
45–59	82	15.0
60	38	15.0
Age cohort for multiple births (YES, ≥ 4 births)		
18–24	4	1.1
25–44	366	35.0
45–59	247	41.0
60	186	67.9
Number of miscarriages (mean, 1.0; 95% CI, 1.0–1.1)		

Variable	N	%
None	518	42.5
1–3	645	52.9
4	57	4.7
Maximum	19	
Currently in menopause *	105	7.0
Completed menopause	618	27.7
Age at menopause, [†] yrs (mean, 45.7; 95% CI, 45.0–46.5)		
18–39	108	18.6
40–51	333	57.2
52	141	24.2
Had hysterectomy [†]	207	33.7
Had oophorectomy	231	10.2

Note: $p < .05$ for all age cohort trends.

* Of those participants who reported a menstrual period in the last 12 months ($n = 1,499$).

[†] Of those participants who had gone through menopause (reported that their periods stopped permanently; $n = 618$).

Table 3

Contraceptive Use Characteristics of Alaska Native Women, Alaska EARTH Study, 2004 to 2006

Variable	N	%
Used hormone replacement therapy *		
Yes, currently	100	11.5
Yes, but not now	269	31.0
No	499	57.5
Number of years using hormone replacement therapy *		
<1	74	22.7
1–4	128	39.3
5–10	64	19.6
11	60	18.4
Ever taken birth control pills for 1 month		
Yes, currently	236	10.3
Yes, but not now	1,189	52.0
No	860	37.6
Number of years taken birth control pills		
<1	418	31.0
1–4	508	37.7
5–10	288	21.4
11	134	9.9
Ever taken birth control shots such as Depo Provera		
Yes, currently	137	6.0
Yes, but not now	551	24.0
No	1,612	70.1
Number of years taken birth control shots		
1	261	38.9
2	307	45.8
3	103	15.4
Ever had birth control implant such as Norplant		
Yes, currently	23	1.0
Yes, but not now	203	8.8
No	2,069	90.2
Number of years had birth control implant		
<1	59	28.9
1–4	88	43.1
5–10	53	26.0
11	4	2.0

* Including estrogen, progesterone, or other female hormones by pill, injection, or patch but not including hormones used for birth control ($n = 868$).