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Birth Weight and Subsequent Risk of Cancer

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Abstract

Background—We aimed to determine the association between self-reported birth weight and incident cancer in the Women’s Health Initiative Observational Study cohort, a large multiethnic cohort of postmenopausal women.

Methods—65,850 women reported their birth weight by category (<6 lbs., 6 lbs.–7 lbs. 15 oz., 8 lbs.–9 lbs. 15 oz., and 10 lbs.). All self-reported, incident cancers were adjudicated by study staff. We used Cox proportional hazards regression to estimate crude and adjusted hazard ratios (aHR) for associations between birth weight and: 1) all cancer sites combined, 2) gynecologic cancers, and 3) several site-specific cancer sites.

Results—After adjustments, birth weight was positively associated with the risk of lung cancer ($p=0.01$), and colon cancer ($p=0.04$). An inverse trend was observed between birth weight and risk for leukemia ($p=0.04$). A significant trend was not observed with breast cancer risk ($p=0.67$); however, women born weighing 10 lbs. were less likely to develop breast cancer compared to women born between 6 lbs.–7 lbs. 15 oz (aHR 0.77, 95% CI 0.63, 0.94).

Conclusion—Birth weight category appears to be significantly associated with the risk of any postmenopausal incident cancer, though the direction of the association varies by cancer type.

Keywords

birth weight; neoplasms; breast neoplasms; colorectal neoplasms; lung neoplasms; ovarian neoplasms; endometrial neoplasms; leukemia

1. INTRODUCTION

Cancer is a complicated set of diseases with complex and multifactorial etiology. Known risk factors for various cancers only partly explain cancer incidence among adult populations. While genetic factors play a role in cancer development, there is a general agreement that non-genetic factors, including tobacco smoke, air pollutants, certain viruses and bacteria, occupational hazards, and dietary factors contribute to cancer causation.¹ It has also been suggested that the *in utero* environment, including suboptimal growth during the prenatal period, impacts adult health². The Developmental Origins of Health and Disease hypothesis (also known as the “fetal origins hypothesis” or “Barker hypothesis”) suggests that chronic conditions or disorders in later life result from developmental programming, including fetal malnutrition and other adverse influences *in utero* that permanently set, or “program”, the structure and function of different organs and organ systems.² This programming may lead to the impairment of key physiologic and metabolic systems that have been linked to cancer and other chronic diseases: the immune system, inflammation,

quantity and quality of stem cells, anti-oxidant defenses, and neuro-endocrine settings.³ Large cohort studies have shown a consistent relationship between smaller birth weight and increased risk of type 2 diabetes^{4,5} and heart disease^{6,7}, while larger birth weight has been associated with an increased risk of obesity.⁸ However, the relationship between weight at birth and adult cancer is not as well established, likely due, in part, to multiple cancer sub-types and complex etiology.

The association between increasing birth weight and increased risk for premenopausal breast cancer has been well established, though this has been demonstrated primarily among Caucasian premenopausal women.^{9,10} The association between birth weight and the risk for breast cancer in postmenopausal women is not as well established. Authors of a recent meta-analysis examining the association between birth weight and breast cancer performed a sub-analysis stratifying the included studies by pre-menopausal (9 studies) and post-menopausal (5 studies) status of the women. They found that the odds of premenopausal breast cancer in women born in the highest birth weight category (>4,000 g) was non-significantly increased (OR 1.37, 95% CI 0.98–1.92) compared to women born in the lowest birth weight category (<2,500 g or 3,000 g). The odds of developing post-menopausal breast cancer was 1.13 (95% CI 0.85–1.51) for those in the highest birth weight category compared to those in the lowest birth weight category.¹⁰ While there was some similarity in the nonsignificant summary measures for both pre-and post-menopausal disease, there was statistical heterogeneity among the studies for each summary measure.

Except for studies of breast cancer⁹, few have examined the association of birth weight with all-site cancers and other site-specific cancer types, and the findings have been inconsistent.^{11–14} While several studies evaluating the relationship of birth weight and cancer mortality have been performed,^{11–14} to our knowledge, only 3 studies published to date have addressed the possible role of birth weight in the development or incidence of all-site cancers.^{1,15,16} One study found an overall 7% increase in all-site cancer risk per 1,000 gram increase in birth weight.¹⁵ The other two studies also found a positive association between birth weight and cancer risk.^{1,16} However, two of the studies were unable to adjust for potential covariates due to their study design,^{15,16} and all three study populations were limited to individuals of European ancestry.^{17,18} Additionally, many of the studies that evaluate the association between birth weight and cancer risk are comprised of premenopausal women; and inconsistent findings have been reported in the studies that stratify by menopausal status.¹⁶

Thus, in the current study, we examined the association between birth weight and 1) all cancers combined, (2) gynecologic cancers combined, and (3) selected site-specific cancers, using the Women's Health Initiative (WHI) Observational Study (OS), a multi-ethnic cohort of postmenopausal women.

2. MATERIALS AND METHODS

2.1 Study Population

The WHI is a large, long-term national health study that was designed to advance knowledge of the determinants of major chronic diseases in postmenopausal women.

Detailed information regarding the study's recruitment, eligibility, and implementation, has been described elsewhere.¹⁹ Briefly, 161,608 postmenopausal women between the ages of 50–79 years representing major racial/ethnic groups were recruited from the general population at 40 US clinical centers between 1993 and 1998. Women could have enrolled into overlapping clinical trials (WHI-CT; N=67,932) or the long-term follow-up observational study (WHI-OS; N=93,676). As only the participants in the observational study reported their birth weight, our analysis was restricted to these women. All women provided written informed consent at study initiation, and the study protocols were approved by the Institutional Review Board of each participating clinical center.²⁰

2.2 Data collection of baseline measurements

At study entry, all women completed self-administered, structured questionnaires used to collect information on demographics, medical, reproductive, and family history, and dietary and lifestyle factors. Women were asked to report their birth weight as one of the following categories: unknown, less than 6 pounds (lbs.), 6 lbs. to 7 lbs. 15 ounces (oz.), 8 lbs. to 9 lbs. 15 oz., and 10 or more lbs. Women were also asked to report if they were a twin or triplet and if they were born 4 or more weeks premature. In addition, physical measurements of weight, height, and waist and hip circumference, were measured and recorded by trained staff at baseline.

2.3 Follow-up for Cancer Diagnoses

Clinical outcomes, including incident cancer diagnoses, were reported by participants annually through in-person, mailed, or telephone questionnaires, over a mean follow-up time of 11.3 years. Study physicians adjudicated self-reports of malignancy by reviewing the medical records and pathology reports; all cancers were documented and coded according to their primary site and recurrent cancers were not included.²¹ The National Death Index was periodically searched to identify deaths of participants lost to follow-up. Incident cancer cases were analyzed as all adjudicated cancer sites combined, gynecologic cancers (ovarian, endometrial, vaginal, vulvar, cervical, and uterus not otherwise specified), and site-specific cancers with a minimum of 225 reported cases.

2.4 Study Exclusions

For this analysis, women were excluded if they reported being a twin or triplet (n=1,930), were born premature (n=6,849), or had a missing birth weight category (n=11,742). Women who had been previously diagnosed with cancer prior to enrollment in WHI were also excluded from the analysis (n=10,305).

2.5 Statistical Analysis

We examined the baseline characteristics of study subjects across cancer types using chi-square tests for categorical variables and t-tests for continuous variables. Subjects with any incident cancers were compared to those without a diagnosis of incident cancer. In site-specific analyses, women with a specific cancer diagnosis were compared to women who did not develop any cancer over the follow-up period. Cox proportional hazards regression models were used to estimate hazard ratios (HR) and their associated 95% confidence

intervals (95% CI) for associations between cancer (any cancer and site specific) and birth weight with and without adjusting for other potential risk factors, along with a test for trend. For birth weight, we used the “6 lbs. to 7 lbs. 15 oz.” category as the referent group as term infants born within this weight range are considered to be of normal birth weight. Covariates selected for inclusion in the models were well-known risk factors for most cancer types, including demographic characteristics (age, race/ethnicity, education, and normalized socioeconomic status (NSES; defined elsewhere²²) and lifestyle factors (body mass index (BMI) at study baseline, smoking, and alcohol use). All statistical tests were two-sided, and p-values <0.05 were considered statistically significant. Each outcome was considered independently with birth weight; therefore, we did not correct for multiple testing. All analyses were performed using SAS 9.3 (SAS Institute Inc., Cary, NC, USA).

3. RESULTS

During follow-up, 9,324 eligible women with an incident cancer diagnosis and 56,526 eligible women who did not develop any incident cancers were identified. The average age of study participants was 63.0 years at baseline, and the study population was 84.8% Caucasian, 7.4% African American, 2.6% Asian/Pacific Islander, and 1.4% other/unknown race. At baseline, women who later developed an incident cancer were significantly older, were more educated, and had a higher NSES than those who did not develop cancer during the follow-up period (Table 1). Women with an incident cancer were also more likely to be white, be a current or past smoker, and more likely to be a current alcohol user.

Table 2 shows the crude and demographic- and lifestyle-adjusted risks of selected cancers by category of birth weight. Birth weight was significantly and positively associated with the risk of any cancer (all sites combined) (unadjusted, $p=0.0002$). The test for trend remained significant after adjustment for age, race, education, and NSES ($p=0.04$), but dissipated after additional adjustment for BMI, smoking, and alcohol use ($p=0.59$). Similarly, gynecologic cancers and endometrial cancer also exhibited significant positive trends after adjustment for demographic factors ($p=0.04$ and $p=0.04$, respectively), but dissipated after adjustment for other lifestyle adjustments ($p=0.21$ and $p=0.14$, respectively). A positive association and trend was also observed for lung cancer (adjusted, $p=0.01$) and colon cancer ($p=0.04$). A significant, negative trend was observed between birth weight and risk for leukemia (adjusted, $p=0.004$). A significant trend was not observed with breast cancer risk (adjusted, $p=0.54$); however, women born weighing more than ten pounds were significantly less likely to develop breast cancer when compared to women born between 6 lbs. –7 lbs. 15 oz. (adjusted HR 0.77, 95% CI 0.63, 0.94). No significant associations were observed between birth weight and ovarian cancer, pancreatic cancer, non-Hodgkin's lymphoma, or melanoma.

Because the sample sizes decreased substantially with the addition of covariates, we performed sensitivity analyses on all of the univariate and demographics-adjusted models using only those subjects who were included in the final lifestyle-factor adjusted models in order to insure that results were similar with and without those subjects. None of the results were determined to be different.

4. Age at menarche and age at menopause are both important variables to consider when conducting analyses on the risks for breast, endometrial, and ovarian cancers. Because of this, we also performed sensitivity analyses for these three cancer types in which we further adjusted for age at menarche and age at menopause in the models adjusting for demographic and lifestyle factors. For all three cancer types, the results of the sensitivity analyses were identical to the results from the models only containing the demographic and lifestyle factors (data not shown).

DISCUSSION

In this well-established large cohort of postmenopausal women, we found that heavier birth weights were associated with a higher risk of incident cancer, gynecologic cancers, colon cancer, endometrial cancer, and lung cancer. A negative relationship was observed between heavier birth weights and the risk of incident leukemia. Women born in the highest birth weight category had a significantly decreased risk for developing incident breast cancer compared to women born at a normal birth weight.

To our knowledge, only 3 other studies published to date have investigated the association between birth weight and the overall risk of cancer. In a retrospective Swedish cohort of 1,080 women aged 16–48 years, Andersson et al. detected a positive linear association between birth weights and all-site cancer incidence.¹ While this study did have original midwife records from which to obtain the subject's birth weight, it was limited due to its size of only 262 cancer cases and may not be generalizable due to selection of subjects residing in one city (Göteborg) at the start of the study.¹ A second, larger, prospective study of over 11,000 men and women from Sweden (follow-up from November 1960–December 2001) detected a positive linear association between both continuous and categorized birth weight and cancer risk in men and in women less than 50 years of age, but did not find an association with incident cancer risk among women more than 50 years old.¹⁶ However, the study may have been underpowered to detect an association among the older age group (sample sizes were not reported for each age stratification). Finally, Ahlgren et al. conducted a large retrospective cohort study of over 217,000 Danish men and women born between 1930 and 1975 (nearly 7 million person-years of follow-up) aged 6 to 60; a positive linear trend between birth weight and cancer risk was also observed.¹⁵ In this study, however, the authors did not adjust for covariates. A limitation of all three studies is that their study populations were primarily northern European and lacking in racial and ethnic diversity. While our study did not have enough power to stratify by racial group, over 17% of our study population was comprised of women from other racial groups.

An extensive body of research has examined the association between increasing birth weight and breast cancer risk, primarily among premenopausal women or women under 50 years old.^{1,9,10,1523–252627,28} In our study, however, we observed a significant protection from incident cancer among women born 10 pounds at birth, compared to the breast cancer risk among women born at a normal birth weight.

Most studies that performed separate analyses on women with postmenopausal breast cancer have observed different patterns in risk associated with birth weight than those that

evaluated the risk of premenopausal breast cancer.^{16,29–35} In one study conducted by McCormack et al., women were stratified by <50 or ≥50 years of age at time of diagnosis¹⁶; in the latter group, there was a protective association, albeit non-significant, of higher birth weight and the risk of breast cancer. Sanderson et al. also observed the same protective association across birth weight categories in post-menopausal women, though their results were also non-significant. Because the WHI enrolled only postmenopausal women, we were able to analyze a much larger population of women diagnosed with breast cancer after menopause than the previous studies. We found a similar and significant decreased risk for breast cancer among postmenopausal women with larger birth weights (>10 lbs.). This is in contrast to many findings that have been conducted in younger pre-menopausal women where increasing birth weight is a risk factor for breast cancer.¹¹

In addition to examining incident breast cancer risk, we were also able to investigate the association between birth weight and breast cancer at initial study recruitment. Women were asked to self-report their cancer history at baseline and, while we excluded these women from incident cancer analyses, we were able to examine the relationship between birth weight and the risk of breast cancer prior to entry into WHI. In this analysis, we observed an increasing risk for breast cancer with increasing birth weight, though non-significant (data not shown), similar to previous studies examining the association between birth weight and breast cancer risk in younger populations.^{9,10,36} Unfortunately, we do not know the age at which the women developed these cancers, nor do we know their menopause status at their cancer's onset; however, the group of women, as a whole, would have been younger than they were at WHI entry. The possibility of a different impact of birth weight on breast cancer risk in premenopausal and postmenopausal women could be interpreted as etiopathogenic evidence, adding to an already well-known diversity between the two groups in terms of cancer biologic features.³²

There is biologic evidence that larger birth size may be indicative of a greater number of cells at risk of carcinogenesis.^{16,37} Low birth weight can be a reflection of a poor intrauterine environment or impaired fetal nutrition; it can also be a product of maternal complications during pregnancy, such as intrauterine growth restriction, preeclampsia, or preterm birth. Intrauterine conditions may cause lifelong alterations of key hormonal axes, such as the hypothalamic-pituitary-adrenal axis.¹⁴ Additionally, in utero programming of the insulin-like growth factor (IGF) system may also lead to increased rates of postnatal cell proliferation.³⁸ Higher IGF-1 levels have been shown to increase the risk of epithelial cancers, and increasing birth weight has been shown to positively correlate with IGF-1 levels in adulthood.³⁹ This evidence, along with our finding of increasing birth weight associated with increased risk of any cancer, many of which are epithelial cancers, suggests this risk may be mediated through IGF.

One exception to this trend of increasing cancer risk with increasing birth weight was observed for leukemia. Women born < 6 lbs. had a significantly higher risk for developing incident leukemia, the only evaluated cancer in which being born weighing < 6 lbs. was a significant risk factor. Risk for leukemia subsequently decreased (though not significantly) with increasing birth weight. This result was unexpected, as previous studies found higher birth weights to be associated with higher risk of childhood leukemias^{40–42} and adult

leukemias.¹⁵ However, it has already been suggested that the two leukemias are very different with respect to their etiologies and epidemiology, and this result adds further evidence of this difference.⁴³

Strengths of our study include its prospective design and large sample size, which allowed us to observe a considerable number of cancer cases. In addition, all of the cancer cases that occurred after entry into WHI were adjudicated, a quality not feasible in most studies. We were also able to evaluate a broad spectrum of potential confounders that may account for the underlying association between birth weight and cancer risk.

Our study was limited to evaluating only categories of birth weight based on the woman's self-report. While this is a less than ideal method compared to use of birth weights abstracted from birth certificates or medical records, validity has been demonstrated for the correlation of categories of self-reported birth weight to medical record information.^{44,45} While the validity of self-reported birth weight might be expected to be lower in an older population such as WHI, the Danish Nurse's Health Study was able to confirm that self-reported birth weight was consistent with birth records in older women.⁴⁴ Additionally, any bias that results from the potential misclassification of the exposure would be nondifferential. Only cases of cancer that occurred after enrollment into WHI were adjudicated by trained adjudicators. While we only considered incident cases of cancer that were diagnosed after entry into WHI in the main analysis, the sub-analysis of cancers diagnosed prior to enrollment was based on self-reports without confirmation or adjudication, which could result in misclassification. Another limitation of these analyses was our inability to adjust for all of the covariates believed to be potentially important in the pathophysiology of many of the site-specific cancers. While we did analyze many of the cancer subgroups adjusting for lifestyle factors, the number of cases with complete data on all covariates was substantially reduced and fewer subjects were available for analysis in the <6lbs. and 10 lbs. birth weight categories. It should also be noted that there has been a great deal of criticism in the life course epidemiology field as to whether or not statistical adjustments for adult lifestyle factors such as BMI should be included in models examining birth weight and later-life chronic conditions such as cancer as they may be over-adjusting.⁴⁶ For example, because adult BMI is, in part, a function of birth weight, it is often seen as inappropriate to adjust for this variable as a confounder.⁴⁷ Thus, it is suggested that relationships between birth weight and chronic diseases of adulthood be presented unadjusted as well as adjusted for intermediates.⁴⁸ We did indeed see that many significant trends diminished when adjusting for adult lifestyle factors; this could be a result of loss of power in these analyses, true confounding, or over-adjustment by inclusion of later-life lifestyle factors. Sub-analyses stratified by race/ethnic group were also attempted with similar results; however, the analysis lacked sufficient power and no pertinent conclusions could be drawn. We also did not have data on *in utero* pregnancy-related exposures and conditions as this information was not collected (e.g. *in utero* tobacco smoking exposure; gestational diabetes).

Birth weight category appears to be significantly associated with the risk of any postmenopausal incident cancer, though the direction of the association varies by specific cancer type. To our knowledge, this is the largest study of birth weight and adult cancer

incidence in postmenopausal women in a multi-ethnic cohort to date. Future research needs to further focus on racial disparities in the birth weight and cancer relationship, as we were unable to evaluate the association in specific racial groups. Further examinations into possible site-specific associations should also be pursued.

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Research Highlights

- We examined for an association between birth weight and several postmenopausal cancer types
- Birth weight was positively associated with the risk of gynecologic, lung, endometrial, and colon cancer.
- Birth weight was negatively associated with the risk of leukemia
- Women born weighing ≥ 10 lbs. were less likely to develop breast cancer compared to women born between 6 lbs.–7 lbs. 15 oz.

Table 1

Baseline characteristics of 60,848 WHI study participants by cancer status

	Any Cancer n= 9,324	No Cancer n= 56,526	p ^a
Birth weight			
< 6 lbs	688 (7.4)	4823 (8.5)	<0.0001
6–7.99 lbs	6298 (67.6)	38 495 (68.1)	
8–9.99 lbs	2031 (21.8)	11 274 (19.9)	
10 lbs	307 (3.3)	1934 (3.4)	
Age at baseline (mean, std)	64.0 (7.1)	62.9 (7.3)	<0.0001
Race/ethnicity			
White	8398 (90.3)	47 429 (84.1)	<0.0001
Black	475 (5.1)	4422 (7.8)	
Asian/Pacific Islander	161 (1.7)	1532 (2.7)	
Hispanic	171 (1.8)	2142 (3.8)	
Other/Unknown	95 (1.0)	852 (1.5)	
Education			
High school diploma/GED	1633 (17.6)	11 514 (20.5)	<0.0001
School after high school	3331 (36.0)	20 573 (36.7)	
College degree or higher	4301 (46.4)	23 988 (42.8)	
Normalized socioeconomic status (NSES)	76.9 (7.8)	76.1 (8.5)	<0.0001
BMI at baseline (mean, std)	27.3 (5.8)	27.2 (5.8)	0.24
Smoking status			
Never	4219 (45.8)	28 770 (51.5)	<0.0001
Past	4316 (46.9)	23 712 (42.4)	
Current	676 (7.3)	3390 (6.1)	
Alcohol use			
Non-drinker	788 (8.5)	6161 (11.0)	<0.0001
Past drinker	1515 (16.3)	10 314 (18.3)	
Current drinker	6989 (75.2)	39 753 (70.7)	

Numbers are N (%) or categorical variables or mean (standard deviation) for continuous variables

^aP-values are from t-tests and chi-square statistics and compare that particular cancer category to the women with “no cancer”

Table 2

Relationship of birth weight to cancer among women in the Women's Health Initiative

	Birth weight Category					P for Trend
	< 6 lbs HR (95% CI)	6–7.9 lbs HR (95% CI)	8–9.9 lbs HR (95% CI)	10 lbs HR (95% CI)		
<i>n</i>	5,511	44,793	13,305	2,241		
All sites (<i>n</i> cases)	688	6,298	2,031	307		
Unadjusted (Cases = 9,733)	0.90 (0.84, 0.98)	1.00 (Ref)	1.08 (1.03, 1.13)	1.01 (0.91, 1.13)	0.0002	
+ Demographics ^a (Cases = 8,692)	0.93 (0.86, 1.01)	1.00 (Ref)	1.07 (1.01, 1.12)	0.94 (0.84, 1.06)	0.04	
+ Lifestyle Factors ^b (Cases = 6,898)	0.95 (0.86, 1.04)	1.00 (Ref)	1.03 (0.97, 1.09)	0.92 (0.80, 1.05)	0.59	
Breast cancer (<i>n</i> cases)	314	2,804	880	113		
Unadjusted (Cases = 4,103)	0.93 (0.83, 1.05)	1.00 (Ref)	1.05 (0.97, 1.13)	0.82 (0.68, 0.99)	0.66	
+ Demographics ^a (Cases = 3,678)	0.94 (0.83, 1.06)	1.00 (Ref)	1.03 (0.95, 1.11)	0.76 (0.62, 0.94)	0.67	
+ Lifestyle Factors ^b (Cases = 2,913)	0.95 (0.84, 1.08)	1.00 (Ref)	1.02 (0.94, 1.11)	0.77 (0.63, 0.94)	0.54	
Colon Cancer (<i>n</i> cases)	43	463	176	21		
Unadjusted (Cases = 710)	0.77 (0.56, 1.05)	1.00 (Ref)	1.28 (1.08, 1.53)	0.92 (0.59, 1.42)	0.007	
+ Demographics ^a (Cases = 625)	0.75 (0.53, 1.05)	1.00 (Ref)	1.28 (1.06, 1.54)	0.83 (0.53, 1.32)	0.03	
+ Lifestyle Factors ^b (Cases = 604)	0.69 (0.48, 0.98)	1.00 (Ref)	1.23 (1.02, 1.48)	0.81 (0.51, 1.29)	0.04	
Endometrial Cancer (<i>n</i> cases)	32	396	153	< 20 ^d		
Unadjusted (Cases = 599)	0.67 (0.47, 0.96)	1.00 (Ref)	1.29 (1.07, 1.56)	0.72 (0.42, 1.22)	0.01	
+ Demographics ^a (Cases = 536)	0.71 (0.49, 1.04)	1.00 (Ref)	1.30 (1.07, 1.59)	0.62 (0.34, 1.13)	0.04	
+ Lifestyle Factors ^b (Cases = 522)	0.71 (0.48, 1.04)	1.00 (Ref)	1.26 (1.04, 1.54)	0.54 (0.29, 1.01)	0.14	
Gynecologic cancers ^c (<i>n</i> cases)	65	694	265	34		
Unadjusted (Cases = 1,051)	0.80 (0.62, 1.03)	1.00 (Ref)	1.30 (1.13, 1.50)	0.96 (0.67, 1.36)	0.0008	
+ Demographics ^a (Cases = 939)	0.89 (0.69, 1.16)	1.00 (Ref)	1.25 (1.08, 1.46)	0.86 (0.59, 1.27)	0.04	
+ Lifestyle Factors ^b (Cases = 740)	0.95 (0.71, 1.27)	1.00 (Ref)	1.20 (1.01, 1.43)	0.85 (0.55, 1.32)	0.21	
Leukemia (<i>n</i> cases)	30	170	47	< 20 ^d		
Unadjusted (Cases = 260)	1.54 (1.06, 2.25)	1.00 (Ref)	0.90 (0.65, 1.24)	0.83 (0.39, 1.76)	0.04	
+ Demographics ^a (Cases = 228)	1.71 (1.15, 2.52)	1.00 (Ref)	0.89 (0.63, 1.25)	0.64 (0.26, 1.55)	0.01	

	Birth weight Category					P for Trend
	< 6 lbs HR (95% CI)	6–7.9 lbs HR (95% CI)	8–9 lbs HR (95% CI)	10 lbs HR (95% CI)		
+ Lifestyle Factors ^b (Cases = 222)	1.77 (1.19, 2.62)	1.00 (Ref)	0.88 (0.62, 1.25)	0.51 (0.19, 1.39)	0.004	
Lung cancer (<i>n</i> cases)	60	594	207	46		
Unadjusted (Cases = 915)	0.87 (0.72, 1.05)	1.00 (Ref)	1.12 (0.99, 1.26)	1.44 (1.14, 1.80)	0.0001	
+ Demographics ^a (Cases = 819)	0.82 (0.61, 1.09)	1.00 (Ref)	1.13 (0.96, 1.33)	1.42 (1.03, 1.94)	0.003	
+ Lifestyle Factors ^b (Cases = 800)	0.80 (0.60, 1.08)	1.00 (Ref)	1.10 (0.93, 1.30)	1.36 (0.99, 1.88)	0.01	
Lymphoma - non-Hodgkin's (<i>n</i> cases)	27	312	84	20		
Unadjusted (Cases = 446)	0.72 (0.48, 1.06)	1.00 (Ref)	0.89 (0.70, 1.13)	1.30 (0.83, 2.05)	0.33	
+ Demographics ^a (Cases = 399)	0.83 (0.55, 1.24)	1.00 (Ref)	0.94 (0.73, 1.21)	1.13 (0.69, 1.85)	0.63	
+ Lifestyle Factors ^b (Cases = 388)	0.83 (0.55, 1.25)	1.00 (Ref)	0.95 (0.74, 1.22)	1.17 (0.71, 1.91)	0.55	
Melanoma (<i>n</i> cases)	44	446	146	21		
Unadjusted (Cases = 664)	0.82 (0.60, 1.12)	1.00 (Ref)	1.10 (0.92, 1.33)	0.96 (0.62, 1.49)	0.18	
+ Demographics ^a (Cases = 585)	0.85 (0.61, 1.19)	1.00 (Ref)	1.08 (0.89, 1.32)	1.01 (0.64, 1.60)	0.28	
+ Lifestyle Factors ^b (Cases = 566)	0.89 (0.64, 1.25)	1.00 (Ref)	1.06 (0.87, 1.30)	1.05 (0.66, 1.67)	0.37	
Ovarian Cancer (<i>n</i> cases)	27	246	96	< 20 ^d		
Unadjusted (Cases = 392)	0.95 (0.64, 1.40)	1.00 (Ref)	1.34 (1.06, 1.69)	1.50 (0.93, 2.41)	0.007	
+ Demographics ^a (Cases = 349)	1.09 (0.74, 1.62)	1.00 (Ref)	1.23 (0.95, 1.58)	1.40 (0.84, 2.32)	0.13	
+ Lifestyle Factors ^b (Cases = 344)	1.12 (0.76, 1.66)	1.00 (Ref)	1.21 (0.94, 1.56)	1.41 (0.85, 2.35)	0.17	
Pancreatic Cancer (<i>n</i> cases)	< 20 ^d	155	57	< 20 ^d		
Unadjusted (Cases = 239)	0.86 (0.51, 1.44)	1.00 (Ref)	1.22 (0.90, 1.65)	1.32 (0.70, 2.51)	0.09	
+ Demographics ^a (Cases = 213)	1.00 (0.59, 1.69)	1.00 (Ref)	1.26 (0.92, 1.74)	1.32 (0.70, 2.52)	0.16	
+ Lifestyle Factors ^b (Cases = 207)	0.97 (0.57, 1.65)	1.00 (Ref)	1.24 (0.90, 1.72)	1.18 (0.60, 2.32)	0.24	

^a Demographic factors include age, race, education, and normalized socioeconomic status

^b Lifestyle factors include BMI, smoking status, and alcohol use

^c Gynecologic cancers include cervical, endometrial, ovarian, vaginal, and uterine (otherwise unspecified) cancers

^d Policy from the Women's Health Initiative will not allow researchers to report numbers of participants in cells less than 20. As such, cells that contain fewer than 20 participants read "< 20"