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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, 6–7 lbs 15 oz, 8–9 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.

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 health [2]. 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

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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 (>4000 g) was non-significantly increased (OR 1.37, 95% CI 0.98–1.92) compared to women born in the lowest birth weight category (<2500 g or 3000 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 cancer [9], 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]. Whiles 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 1000 g 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), 6–7 lbs 15 ounces (oz), 8–9 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 ($n = 1930$), were born premature ($n = 6849$), 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