A BRIEF ORIGINAL CONTRIBUTION

Retrospective Analysis of Birth Weight and Prostate Cancer in the Health Professionals Follow-up Study

Elizabeth A. Platz,1,2 Edward Giovannucci,1,4 Eric B. Rimm,1,2,4 Gary C. Curhan,1,4,5 Donna Spiegelman,2,3 Graham A. Colditz,2,4 and Walter C. Willett1,2,4

The authors retrospectively evaluated the relation between birth weight and prostate cancer (1986–1994) among 21,140 men of the Health Professionals Follow-up Study who reported in 1994 their weight at birth. No relation between birth weight and prostate cancer (n = 545) was observed in multivariate logistic models. For high stage/grade tumors (n = 213), compared with birth weights <7.0 lbs (<3,175 g), the relative risks were 1.20 (95% confidence interval (CI) 0.79–1.83) for 8.5–9.9 lbs (3,855.6–4,490.6 g) and 1.30 (95% CI 0.80–2.10) for ≥10 lbs (≥4,536 g). These findings do not support an overall association between birth weight and prostate cancer incidence, but the possibility of a modest positive association between birth weight and high stage/grade prostatic cancer cannot be excluded.


birth weight; cohort studies; prostatic neoplasms

Ross and Henderson (1) recently hypothesized that the hormonal environment in utero plays an etiologic role in the development of prostate cancer decades later. Tibblin et al. (2) addressed this hypothesis by evaluating whether birth weight, as a marker of this environment, predicted prostate cancer incidence in a cohort of 366 men born in Sweden in 1913 and in which 21 prostate cancer cases were identified since 1963. Notably, prostate cancer incidence appeared to be more than four times higher among those whose birth weight was in the upper compared with the lower quartile. Subsequently, in a Swedish nested case-control study, Ekbom et al. (3) found a modest, non-statistically significant, positive association between birth weight and incidence of prostate cancer (per 500 g, relative risk (RR) = 1.04, 95 percent confidence interval (CI) 0.88–1.23) or death from the dis-

case (per 500 g, RR = 1.22, 95 percent CI 0.87–1.70). Because of these intriguing findings in Swedish studies, we examined the relation between birth weight and prostate cancer incidence in a large cohort of US male health professionals followed since 1986.

MATERIALS AND METHODS

The Health Professionals Follow-up Study consists of 51,529 men 40–75 years of age who at enrollment in 1986 completed a questionnaire that included demographic information, medical history, and diet. Cohort follow-up and identification and confirmation of prostate cancer cases have been described previously (4). In 1994, we asked cohort members to report their birth weight in pounds in the following categories: <5.5, 5.5–6.9, 7–8.4, 8.5–9.9, ≥10 lbs, or unknown. The Spearman correlation between self-reported birth weight among men whose mothers were living (n = 3,803) and maternal reports was 0.72 (p < 0.001) (5).

Among the men at baseline without a prior cancer diagnosis and who had a valid diet report (n = 46,588), 1,375 cases of prostate cancer were confirmed during the period from 1986 to 1994, and of these, 545 provided birth weight in 1994. Birth weight was unknown for the remaining cases for the following reasons: 96 responded to the short form of the 1994 questionnaire, which did not include the question on birth weight; 532 responded, but reported not knowing their birth weight; 26 responded, but did not
answer the question on birth weight; and 176 did not respond to the 1994 questionnaire, among whom 96 died before the 1994 questionnaire was sent.

We further classified cases as high stage/grade, if stages C or D, and/or Gleason grade ≥7, because some risk factors may act on progression of tumors, or risk factors for aggressive prostate cancers may differ from nonaggressive (6). We included in the analysis 21,140 men who returned the 1994 questionnaire (n = 38,706) with birth weight reported, who reported plausible dietary intake and other exposure data based on previously reported criteria (4), and who were free of diagnosed cancer in 1986.

Statistical analysis

We estimated the relative risk of prostate cancer by the odds ratio from age-adjusted and multivariate logistic regression models (7), and calculated 95 percent confidence intervals. Multivariate models included baseline (1986) values for age (13 intervals), race (black, Asian, or other/unknown, white), vasectomy (yes/no), diabetes mellitus (yes/no), family history of prostate cancer (yes/no), and quintiles of body mass index (kg/m²), height, and intake of animal fat and lycopene. Because the relative risks were essentially the same for the <5.5 lb (<2,494.8 g) and 5.5–6.9 lb (2,494.8–3,129.8 g) categories, to increase stability for secondary analyses, we used <7.0 lbs (<3,175 g) as the referent in presented analyses. To evaluate trend, we entered the midpoint of each birth weight category as a continuous variable in the logistic models. We used stratified logistic models to evaluate if the association between prostate cancer and birth weight varied by age and height. Because a large number reported that they did not know their birth weight or left the question blank (n = 14,367), we compared the age-standardized distribution of covariates among these men with those who reported a birth weight. We evaluated in a logistic model whether missing birth weight predicted prostate cancer to investigate the potential for selection bias among those with known birth weight. All analyses were conducted using SAS software (SAS Institute, Cary, North Carolina).

RESULTS

Among 21,140 men who reported their birth weight in 1994 and were otherwise eligible, 545 prostate cancer cases were confirmed between 1986 and 1994. Of these, 39.1 percent had high stage/grade tumors. Almost half reported a birth weight of 7–8.4 lbs (3,175.2–3,810.2 g) and 7.5 percent reported a birth weight ≥10 lbs (≥4,536 g). Men who reported a birth weight ≥10 lbs tended to be older, and, after standardizing for age, to have a higher body mass index, to be taller, and to have a family history of prostate cancer compared with those who reported a lower birth weight (table 1).

Men with unknown or missing birth weight (n = 14,367) tended to be older and, after adjusting for age, shorter, less obese, nonwhite, without family history of prostate cancer, and to have had a vasectomy. However, compared with those with a reported birth weight, men with an unknown birth weight did not have an increased risk of total prostate cancer (multivariate RR = 1.02, 95 percent CI 0.90–1.16) or aggressive prostate cancer (RR = 0.95, 95 percent CI 0.77–1.16).

In age-adjusted and multivariate models, no association was seen between birth weight and total prostate cancer (table 2). In multivariate models, compared with men who reported birth weights <7.0 lbs (<3,175 g), a slight elevation in risk at birth weights of 8.5–9.9 lbs (3,855.6–4,490.6 g) (RR = 1.20, 95 percent CI 0.79–1.83) or ≥10 lbs (≥4,536 g) (RR = 1.30, 95 percent CI 0.80–2.10) was seen for high stage/grade cases, although the relation did not show a linear increase (p trend = 0.24). Restricting cases to those whose diagnosis was within 4 years (table 2) or 2 years (not shown) prior to birth weight assessment showed results consistent with the 8-year analysis. In multivariate models, risk of total or high stage/grade prostate cancer associated with birth weight did not vary across levels of age or height.

DISCUSSION

We did not observe a relation between birth weight and prostate cancer in an analysis of 545 cases diagnosed between 1986 and 1994 among 21,140 US men who reported their birth weight in 1994. For high stage/grade tumors, we could not rule out a small positive association at birth weights of ≥8.5 lbs (≥3,855.6 g), which was consistent in magnitude with the findings of Ekbom et al. (3) for death from prostate cancer. Based on our data, however, an elevation in prostate cancer risk of more than fourfold from top to bottom quartile, as observed by Tibblin et al. (2), would seem to be unlikely.

Mechanisms underlying the hypothesized birth weight-cancer relation have been proposed, although they remain speculative. Birth weight may be reflective of circulating concentrations of maternal hormones (8), or maternal supply of nutrients to the fetus yielding altered production of fetal growth factors (9). Ross and Henderson (1) have proposed the hypothesis that maternal level of testosterone may affect the "hypothalamic-pituitary-testicular feedback system"
in the male fetus, resulting in greater lifelong concentrations of circulating testosterone in male offspring. Whether birth weight is a marker of exposure to testosterone during gestation, to our knowledge, has not been explored. Consistent with the hypothesis of Trichopoulos (10) that higher exposure to maternal estrogen in utero confers a greater risk of breast cancer, Ekbom et al. (11) have reported an increasing risk of breast cancer with greater weight at birth.

The major strengths of our analysis include the large number of prostate cancer cases with which to estimate this relation, the assessment separately by total and high stage/grade prostate cancer, and the ability to control for multiple potential confounders. The major limitations were reliance on self-reported birth weight and the retrospective nature of this analysis. Although nondifferential misclassification of true birth weight using self-reports is probable, it is unlikely to be profound. In this cohort, a validation study showed that the men’s self-reports were well correlated with mothers’ reports and that 97.9 percent reported birth weight within one category of their mother (5), and low birth weight was shown to be associated with hypertension and diabetes (5).

To support further that nondifferential misclassification of birth weight was not extreme, we corrected the age-adjusted relative risk for measurement error using mothers’ reports of sons’ birth weight from the validation study (5) as the gold standard and using the regression calibration method (12). Assuming that risk of high stage/grade prostate cancer increases linearly on the natural logarithm scale, the per pound measurement-error-corrected relative risk was 1.11 (95 percent CI 0.98–1.27), compared with the uncorrected estimate of 1.08 (95 percent CI 0.98–1.19). Because the errors in the sons’ and mothers’ reports are likely to be positively correlated, use of the regression calibration method probably understates the deattenuated relative risk. Due to the fact that state birth certificates were not collected and, thus, the correlation in the errors cannot be determined, we refined this correction using values for required parameters from a validation study (n = 220) in the Nurses’ Health Study II (13) that included birth certificates and a method for the case of an “alloyed gold standard” (14). Although Nurses’ Health Study II members are younger and female, the correlation between the mothers’ and daughters’ reports (r = 0.77) was similar to that of the mothers’ and

### TABLE 1. Age-standardized baseline demographic characteristics according to birth weight category among 21,140 men: the Health Professionals Follow-up Study, 1986–1994

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Participants No. 21,140</th>
<th>Birth weight (lbs*)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td>&lt;7</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>21,140</td>
<td>5,888</td>
</tr>
<tr>
<td><strong>Prostate cancer cases (no.)</strong></td>
<td>545</td>
<td>137</td>
</tr>
<tr>
<td>High stage/grade (no.)</td>
<td>213</td>
<td>51</td>
</tr>
<tr>
<td><strong>Age (years), mean (SD)</strong></td>
<td>52.5 (9.1)</td>
<td>52.1</td>
</tr>
<tr>
<td>&lt;50 (%)</td>
<td>43.3</td>
<td>44.4</td>
</tr>
<tr>
<td>50–59 (%)</td>
<td>31.6</td>
<td>31.3</td>
</tr>
<tr>
<td>60–69 (%)</td>
<td>21.2</td>
<td>20.2</td>
</tr>
<tr>
<td>≥70 (%)</td>
<td>3.9</td>
<td>3.7</td>
</tr>
<tr>
<td><strong>Race (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>92.5</td>
<td>91.0</td>
</tr>
<tr>
<td>Black</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Asian</td>
<td>1.0</td>
<td>2.2</td>
</tr>
<tr>
<td>Other/unknown</td>
<td>6.0</td>
<td>6.3</td>
</tr>
<tr>
<td><strong>Family history of prostate cancer (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>2.3</td>
<td>3.1</td>
</tr>
<tr>
<td>Vasectomy (%)</td>
<td>23.7</td>
<td>22.8</td>
</tr>
<tr>
<td>Body mass index (kg/m²), mean (SD)</td>
<td>25.6 (3.2)</td>
<td>25.3</td>
</tr>
<tr>
<td>Height (inches), mean (SD)</td>
<td>70.4 (2.7)</td>
<td>69.6</td>
</tr>
<tr>
<td>Lycopene intake (µg/day), mean (SD)</td>
<td>5,007 (3,772)</td>
<td>5,109</td>
</tr>
<tr>
<td>Animal fat intake (g/day), mean (SD)</td>
<td>41.1 (12.3)</td>
<td>41.0</td>
</tr>
</tbody>
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* 1 Ib = 453.6 g.
† SD, standard deviation.
‡ Either father or brother diagnosed with prostate cancer and reported in 1990.

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<tbody>
<tr>
<td>&lt;7†</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>7–8.4</td>
<td>1.04</td>
<td>1.05</td>
</tr>
<tr>
<td>8.5–9.9</td>
<td>1.18</td>
<td>1.28</td>
</tr>
<tr>
<td>≥10</td>
<td>1.11</td>
<td>1.30</td>
</tr>
<tr>
<td>95% CI</td>
<td>1.00–1.16</td>
<td>1.00–1.14</td>
</tr>
<tr>
<td></td>
<td>0.83–1.28</td>
<td>0.89–1.52</td>
</tr>
<tr>
<td></td>
<td>0.79–1.50</td>
<td></td>
</tr>
<tr>
<td>High stage/grade (no.)</td>
<td>0.72–1.46</td>
<td>0.79–1.83</td>
</tr>
<tr>
<td>RR§</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>RRfl</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.72–1.57</td>
<td>0.79–1.99</td>
</tr>
<tr>
<td></td>
<td>0.71–2.11</td>
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* 1 lb = 453.6 g.
† Referent.
‡ Calculated by entering the midpoint of each birth weight category as a continuous variable in a multiple logistic model. These estimates are not corrected for measurement error in report of birth weight.
§ Relative risk adjusted for age (1986) by logistic regression.
¶ Relative risk adjusted for baseline age, race, family history of prostate cancer (1990), vasectomy, diabetes mellitus, and quintiles of body mass index, height, and intake of animal fat and lycopene by multiple logistic regression.
# CI, confidence interval.

Although birth weight was assessed after cases were diagnosed, because the birth weight-chronic disease hypothesis was largely unknown at the time of self-report, it is unlikely that cases would differently recall their birth weight. Bias due to differential nonreporting by men with the heaviest birth weights is unlikely because babies with birth weights ≥10 lbs (≥4,536 g) are infrequent and it would be expected that knowledge and memory of a large birth weight would exceed that of an average birth weight regardless of current prostate cancer diagnosis. Further, no difference in risk of total or aggressive prostate cancer was evident when we compared men with an unknown birth weight with men with a reported birth weight. Information was not collected on factors that affected birth weight, such as length of gestation, maternal nutrition during pregnancy, or maternal history of gestational diabetes or diabetes mellitus during pregnancy; these factors could confound or modify the birth weight-prostate cancer relation. Finally, if survival to 1994, the year of birth weight report, was poorer among prostate cancer cases with more aggressive tumors related to higher birth weights, then an underestimation of a positive association might have occurred. Because 96 cases died before 1994 and, thus, we could not rule out survival bias, we conducted an analysis restricted to cases diagnosed closer in time to report of birth weight (table 2). Only eight men in the 2-year follow-up period and 44 men in the 4-year follow-up period died before the 1994 questionnaire was sent. Once more, no strong evidence for a positive association with either total or high stage/grade prostate cancer could be detected.

Additional follow-up of the Health Professional Follow-up Study cohort and future prospective analysis will help clarify the birth weight-prostate cancer relation. Nevertheless, these retrospective data do not support a major association between birth weight and prostate cancer risk.

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REFERENCES