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Invited Commentary: Do Anthropometric Measures Predict Risk of Prostate Cancer?

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In this issue of the *Journal*, Schuurman et al. (1) investigate the association between several anthropometric measures and the risk of prostate cancer among approximately 60,000 male participants of the Netherlands Cohort Study. In many ways, their findings echo the results of most previous cohort and case-control studies on this topic in that they are largely inconclusive. As discussed by Schuurman et al., most previous studies of prostate cancer and anthropometric measures (including body mass index, body fat distribution, lean body mass, body mass at a young age, change in body mass, and height) have been null, and significant associations that have emerged in individual studies and for certain subgroups of men have not been seen consistently across studies.

In this most recent investigation, cohort members were followed from baseline (September 1986) through 1992; during this period, approximately 700 new cases of prostate cancer were diagnosed. In both age-adjusted and multivariate case-cohort analyses, no associations were apparent between baseline measures of height, body mass index, or estimated lean body mass and prostate cancer risk, regardless of whether the tumors were localized or advanced. A modest positive association was observed for body mass index at age 20 years (body mass index ≥25 vs. <19, relative risk (RR) = 1.33, 95 percent confidence interval (CI): 0.81, 2.10); this association was stronger for localized prostate tumors than for advanced tumors. In contrast, a small (nonsignificant) inverse association with gain in body mass between age 20 years and age at baseline also was seen. With nearly 700 incident cases, this study represents one of the largest prospective investigations of this topic.

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Abbreviations: CI, confidence interval; IGF, insulin-like growth factor; IGF-I, insulin-like growth factor I; IGFBP-3, insulin-like growth factor-binding protein 3; RR, relative risk.

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Two other large cohort studies of anthropometry and prostate cancer have been published recently (2, 3). In the study by Andersson et al. (2), a retrospective cohort study of 135,000 Swedish construction workers enrolled from 1971 to 1975 and followed through 1991, 2,368 incident prostate cancer cases and 708 deaths from prostate cancer were observed. Information on current height and weight was collected once—at enrollment. Marginal positive associations were seen for all anthropometric measures (measured weight, measured height, body mass index, and estimated lean body mass) and incident prostate cancer (e.g., body mass index >26.2 vs. <22.1, RR = 1.13, 95 percent CI: 0.99, 1.29). Somewhat stronger positive associations were seen for death from prostate cancer and all anthropometric measures (e.g., body mass index >26.2 vs. <22.1, RR = 1.40, 95 percent CI: 1.09, 1.81). In this study, weight at enrollment largely reflects weight in early adulthood, since this was a fairly young cohort, with 32 percent of the person-years contributed by men who were less than age 30 years and 55 percent contributed by those who were less than age 40 at enrollment.

Giovannucci et al. (3) used data from the Health Professionals Follow-up Study to examine the relations between height, body mass index during childhood and adulthood, waist and hip circumferences, and risk of prostate cancer incidence. In this cohort of approximately 50,000 men enrolled in 1986 and followed through 1994, 1,369 cases of incident prostate cancer occurred. All anthropometric measures were reported by the respondents in 1986 or 1987. While adult body mass and waist and hip circumference were unrelated to risk of total, advanced, or metastatic prostate cancer, a higher body mass at age 21 years was strongly related to a decreased risk of advanced and metastatic disease (body mass index ≥26 vs. <20, RR = 0.53, 95 percent CI: 0.33, 0.86). There was no association between adult weight gain (from age 21 to study enrollment) and total or advanced prostate cancer. A positive association was observed between height and risk of total (height ≥74 vs. ≤68 inches, RR = 1.37, 95 percent CI: 1.10, 1.70) and advanced

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(height ≥74 inches vs. ≤68 inches, RR = 1.68, 95 percent CI: 1.16, 2.43) prostate cancer.

These three large, well-conducted, cohort studies illustrate the difficulties of interpreting epidemiologic data regarding anthropometry and prostate cancer risk. Questions regarding the basic nature of associations between exposures and disease remain unanswered. Is the association between adult body mass and prostate cancer positive (2) or null (1, 3)? Or is body mass at a young age the important measure, and if so, is the relation positive (1) or inverse (3)? Is weight gain during adulthood important (1) or not (3)? Is attained adult height positively associated with risk (2, 3) or not (1)? Finally, do any or all of these measures predict more strongly total or localized disease (1), advanced disease (3), or death (2)?

Several explanations may be offered for these inconclusive findings, including the possibility that currently used anthropometric measures, such as body mass and height, are not important predictors of prostate cancer risk. Alternatively, our anthropometric measures may not be accurate enough, we may be measuring the wrong exposure, or we may be measuring the exposure at the wrong time of life. It seems unlikely that measures of body mass index and height are insufficiently accurate to detect a true association with prostate cancer, given that self-reported data on height and weight have been shown repeatedly to predict risk of other diseases. It seems more likely that the important exposures for prostate cancer are not being adequately captured by the anthropometric measures we are currently using in observational epidemiologic studies.

Our interest in the potential relation between prostate cancer and body size is based, in part, on known associations between body size and other cancers, particularly cancers of the colon and breast, and on our current understanding of how body size and adiposity might influence these cancers.

Obesity has been consistently associated with higher risk of colon cancer in men, while much weaker positive associations have generally been seen for women (4, 5). While the reasons for this gender difference are not completely understood, one hypothesis is that the greater tendency for abdominal or central adiposity in men (versus peripheral adiposity in women) may be important. If central adiposity is a stronger predictor of colon cancer risk than peripheral adiposity or general overweight and men are more likely to deposit fat centrally, then body mass index, the exposure measure used in most studies, may be a more accurate indicator of the relevant exposure in men than in women. Support for the role of central obesity on colon cancer comes from a recent prospective study suggesting that waist circumference and waist-to-hip ratio are related strongly to risk of colon cancer and large adenomas in men (6).

Giovannucci (5) has recently proposed that high body mass, and central obesity in particular, may increase colon cancer risk through their effect on insulin production. With excessive calorie consumption and weight gain, tissues become insensitive (resistant) to insulin, and the body compensates by producing more insulin, resulting in a chronic state of hyperinsulinemia. Obesity, particularly abdominal obesity, is a major determinant of insulin resistance and hyperinsulinemia. The hypothesis assumes that exposure to elevated blood levels of insulin and insulin-like growth factors (IGFs) promote the growth of colon tumors, an assumption that is supported by in vitro studies in colonic mucosal cells and colonic carcinoma cells (7, 8). This hypothesis has received recent empirical support from a prospective case-control study nested in the Physicians' Health Study. Men in the highest quintile for insulin-like growth factor I (IGF-I) had a significantly increased risk of colorectal cancer (RR = 2.51, 95 percent CI: 1.15, 5.46) compared with men in the lowest quintile (9). A strong and significant inverse association was observed for colorectal cancer and IGF-binding protein 3 (IGFBP-3).

Obesity also has been shown consistently to increase the risk of breast cancer in postmenopausal women (10–13). Some studies have found central adiposity to be an independent predictor of postmenopausal breast cancer risk beyond the risk attributed to overweight alone (14, 15). In addition, adult weight gain has been associated with an increased risk for postmenopausal breast cancer, even in studies that did not find an association with relative weight measured at baseline (15–17).

One mechanism for the association between obesity and breast cancer is presumed to be hormonal. Conversion of the androgen precursor androstenedione to estrone in adipose tissue is the primary source of estrogen in postmenopausal women, and levels of circulating estrogens increase with increasing body mass (18). In addition, obesity is strongly and inversely associated with sex hormone-binding globulin, a hormone that reduces the availability of estrogen in the body (18, 19). Thus, overweight, postmenopausal women are exposed to higher levels of endogenous estrogens, which may contribute to their increased risk of breast cancer.

In addition to sex hormones, insulin and/or IGFs may also plays a role in the development of breast cancer. IGF-I is a potent mitogen for breast cancer cells in vitro (20) and is associated with mammary gland hyperplasia (21) and mammary cancer (22) in animals. In addition, IGF-I receptors are present in most human breast tumors at levels approximately 10-fold higher than in normal breast tissue (23). There is evidence that IGF-I can sub-

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stitute for estrogen in stimulating breast cancer proliferation in vitro and in vivo and may mediate estrogenic effects in breast cancer (24). Two case-control studies have found positive associations between plasma IGF-I concentrations and breast cancer (25, 26); in the larger study (26), the association was strongest among premenopausal women, and the magnitude of the association increased when IGF-binding protein 3 (IGFBP-3) was also considered. One prospective study to report this relation (27) observed a strong positive association between plasma IGF-I and breast cancer in premenopausal women, but not in postmenopausal women; again, the association was strengthened with adjustment for IGFBP-3. One other case-control study found that women with early-stage breast cancer had increased circulating insulin levels (as estimated by serum C peptide, a marker of insulin secretion) compared with controls, that this association was independent of general adiposity or abdominal obesity, and that it was seen in both pre- and postmenopausal women (28).

Adult height, independent of weight, has also been shown to be related to both colon and breast cancer (3, 13). While the mechanisms for this observed association are not clear, it may be that early caloric and nutrient restriction, resulting in shorter stature, diminishes cell proliferation or inhibits early tumor events (4). In addition, individuals who attain greater adult height may be exposed to higher levels of IGF-I during childhood and adolescence (3).

As with colon and breast cancer, there is also evidence to support the role of both hormones and IGF-I in prostate carcinogenesis. Prostatic growth and maintenance are dependent on androgens (29), testosterone in high doses induces prostate cancer in rats (30), ablative or antiandrogen therapy is used in treating human prostate cancer (31), and prostate cancer rarely occurs in castrated men (32). In addition, estrogen therapy has a palliative effect on advanced prostate cancer (31), and higher levels of circulating estradiol may be protective (33). Obesity in men is associated with higher estrogen and lower testosterone levels (34, 35); thus, on the basis of this hormonal pattern, one might expect obese men to have lower rates of prostate cancer than do lean men. However, prospective epidemiologic studies examining the relations of circulating hormones (in prediagnostic sera) with subsequent prostate cancer risk are limited, and their results are inconsistent (33, 36–38); men with prostate cancer have not consistently shown higher levels of testosterone, its more potent metabolite dihydrotestosterone, or other androgens. Results from the largest study by Gann et al. (33) support a trend of increasing prostate cancer risk with increasing levels of plasma testosterone and an inverse trend with increasing levels of sex hormone-binding globulin. The inconsistencies among studies may reflect the difficulties of measuring serum/plasma steroid hormones in epidemiologic studies or may reflect our lack of understanding of the complex hormonal influences on this disease and the potential genetic variability in androgen biosynthesis and metabolism in the prostate (39).

The potential influence of IGFs on prostate cancer has been a recent focus of research. As with colon and breast tumors, IGF-I stimulates growth of both tumor and normal cells in the prostate (40). In addition, in both a recent case-control study (41) and a study of prospectively collected blood (42), positive associations were observed between circulating IGF-I levels and prostate cancer risk. In the prospective investigation, 152 cases and 152 controls were selected from the 14,916 members of the Physicians' Health Study who were enrolled and provided plasma in 1982. Follow-up was through 1992 and, on average, 7 years elapsed between plasma collection and diagnosis of prostate cancer in the cases. Men in the highest quartile of IGF-I levels had an RR of 4.3 (95 percent CI: 1.8, 10.6) compared with men in the lowest quartile, independent of baseline prostate-specific antigen levels. This research is promising, and the magnitude of the association is one of the largest yet observed in the study of prostate cancer. However, this study and the recent study of circulating IGF-I and colon cancer (9) bring into question the assumption that measures of body size, such as adult height, weight, and body mass, are directly related to circulating IGFs. No correlation between height, weight, or body mass index and plasma IGF-I was seen in either control group.

What can we conclude at present about the relation between anthropometry and prostate cancer? Unfortunately, we do not yet have answers. While prostate cancer may resemble colon and breast cancer with regard to the evidence supporting hormonal and growth factors as underlying mechanisms of causation, it is proving to be far more complex from an epidemiologic viewpoint. In many ways, it stands in contrast to cancers of the colon and breast, for which there are many established risk factors and several lines of evidence regarding biologic mechanisms that support each other in a reasonably cohesive manner. With the exception of age, race, family history, and possibly dietary fat, epidemiologic studies have been unable to establish risk (or protective) factors for prostate cancer, and at present, this is true for all of the anthropometric factors that have been examined.

Ideally, future investigations will attempt to show that anthropometric risk factors used in observational epidemiologic studies of prostate cancer are related to biochemical measures and that these biochemical mea-

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sures subsequently predict disease in defined populations. In addition, we should continue to conduct studies of prostate cancer that are stage- and perhaps even grade-specific to determine whether risk factors predict differentially for more aggressive disease. As knowledge and measurement of relevant exposures, genetic susceptibility, and their interaction continue to improve in epidemiologic studies, so, it is hoped, will our understanding of the causes of this elusive disease.

REFERENCES

1. Schuurman AG, Goldbohm RA, Dorant E, et al. Anthropometry in relation to prostate cancer risk in the Netherlands Cohort Study. Am J Epidemiol 1999;151:541–9.
2. Andersson SO, Wolk A, Bergstrom R, et al. Body size and prostate cancer: a 20-year follow-up study among 135,006 Swedish construction workers. J Natl Cancer Inst 1997;89: 385–9.
3. Giovannucci E, Rimm EB, Stampfer MJ, et al. Height, body weight, and risk of prostate cancer. Cancer Epidemiol Biomarkers Prev 1997;6:557–63.
4. Potter JD, Slattery ML, Bostick RM, et al. Colon cancer: a review of the epidemiology. Epidemiol Rev 1993;15:499–545.
5. Giovannucci E. Insulin and colon cancer. Cancer Causes Control 1995;6:164–79.
6. Giovannucci E, Ascherio A, Rimm EB, et al. Physical activity, obesity and risk for colon cancer and adenoma in men. Ann Intern Med 1995;122:327–34.
7. Macaulay VM. Insulin-like growth factors and cancer. Br J Cancer 1992;65:311–20.
8. LeRoith D, Baserga R, Helman L, et al. Insulin-like growth factors and cancer. Ann Intern Med 1995;122:54–9.
9. Ma J, Pollak M, Giovannucci E, et al. Prospective study of colorectal cancer in men and plasma levels of insulin-like growth factor (IGF)-I and IGF-binding protein 3. J Natl Cancer Inst 1999;91:620–5.
10. Ballard-Barbash R, Swanson CA. Body weight: estimation of risk for breast and endometrial cancers. Am J Clin Nutr 1996; 63 (Suppl.):437S–41S.
11. Galanis DJ, Kolonel LN, Lee J, et al. Anthropometric predictors of breast cancer incidence and survival in a multi-ethnic cohort of female residents of Hawaii, United States. Cancer Causes Control 1998;9:217–24.
12. Trentham-Dietz A, Newcomb PA, Storer BE, et al. Body size and risk of breast cancer. Am J Epidemiol 1997;145:1011–19.
13. Hunter DJ, Willett WC. Diet, body size, and breast cancer. Epidemiol Rev 1993;15:110– 32.
14. Kaaks R, Van Noord PA, DenTonkelaar I, et al. Breast cancer incidence in relation to height, weight and body-fat distribution in the Dutch "DOM" cohort. Int J Cancer 1998;76: 647–51.
15. Folsom AR, Kaye SA, Prineas RJ, et al. Increased incidence of carcinoma of the breast associated with abdominal adiposity in postmenopausal women. Am J Epidemiol 1990;131:794–803.
16. Huang Z, Hankinson SE, Colditz GA, et al. Dual effects of weight and weight gain on breast cancer risk. JAMA 1997; 278:1407–11.
17. Barnes-Josiah D, Potter JD, Sellers TA, et al. Early body size and subsequent weight gain as predictors of breast cancer incidence (Iowa, United States). Cancer Causes Control 1995;6: 112–18.
18. Madigan MP, Troisi R, Potischman N, et al. Serum hormone levels in relation to reproductive and lifestyle factors in postmenopausal women (United States). Cancer Causes Control 1998;9:199–207.
19. Newcomb PA, Klein R, Klein BEK, et al. Association of dietary and life-style factors with sex hormones in postmenopausal women. Epidemiology 1995;6:318–21.
20. Helle SI, Lonning PE. Insulin-like growth factors in breast cancer. Acta Oncol 1996;35 (Suppl . 5):19–22.
21. Ng ST, Zhou J, Adesanya OO, et al. Growth hormone treatment induces mammary gland hyperplasia in aging primates. Nat Med 1997;3:1141–4.
22. Bates P, Fisher R, Ward A, et al. Mammary cancer in transgenic mice expressing insulin-like growth factor II (IGF II). Br J Cancer 1995;72:1189–93.
23. Papa V, Gliozzo B, Clark GM, et al. Insulin-like growth factor-I receptors are overexpressed and predict a low risk in human breast cancer. Cancer Res 1993;53:3736–40.
24. Dickson RB, McManaway ME, Lippman ME. Estrogen induced factors of breast cancer cells partially replace estrogen to promote tumor growth. Science 1986;232:1540–3.
25. Peyrat JP, Bonneterre J, Hecquet B, et al. Plasma insulin-like growth factor-I (IGF-I) concentrations in human breast cancer. Eur J Cancer 1993;29A:492–7.
26. Bruning PF, Van Doorn J, Bonfrer JMG, et al. Insulin-like growth-factor-binding protein 3 is decreased in early-stage operable pre-menopausal breast cancer. Int J Cancer 1995;62: 266–70.
27. Hankinson SE, Willett WC, Colditz GA, et al. Circulating concentrations of insulin-like growth factor-I and risk of breast cancer. Lancet 1998;351:1393–6.
28. Bruning PF, Bonfrer JMG, van Noord PAH, et al. Insulin resistance and breast cancer risk. Int J Cancer 1992;52:511–16.
29. Henderson BE, Ross BK, Pike MC, et al. Endogenous hormones as a major factor in human cancer. Cancer Res 1982; 42:3232–9.
30. Noble RL. The development of prostatic adenocarcinoma in Nb rats following prolonged sex hormone administration. Cancer Res 1977;37:1929–33.
31. Huggins C, Hodges CV. Studies on prostate cancer: effect of castration, of estrogen, and of androgen injection on serum phosphatase in metastatic carcinoma of the prostate. Cancer Res 1941;1:293–7.
32. Hovenian MS, Deming CL. The heterologous growth of cancer of the human prostate. Surg Gynecol Obstet 1948;86: 29–35.
33. Gann PH, Hennekens CH, Ma J, et al. Prospective study of sex hormone levels and risk of prostate cancer. J Natl Cancer Inst 1996;88:1118–26.
34. Field AE, Colditz GA, Willett WC, et al. The relation of smoking, age, relative weight, and dietary intake to serum adrenal steroids, sex hormones, and sex hormone-binding globulin in middle aged men. J Clin Endocrinol Metab 1994;79:1310–16.
35. Pasquali R, Casimirri F, Cantobelli S, et al. Effect of obesity and body fat distribution on sex hormones and insulin in men. Metabolism 1991;40:101–4.
36. Barrett-Connor E, Garland C, McPhillips JB, et al. A prospective, population-based study of androstenedione, estrogens, and prostatic cancer. Cancer Res 1990;50:169–73.
37. Hsing AW, Comstock GW. Serological precursors of cancer: serum hormones and risk of subsequent prostate cancer. Cancer Epidemiol Biomarkers Prev 1993;2:27–32.
38. Nomura AMY, Stemmermann GN, Chyou P-H, et al. Serum androgens and prostate cancer. Cancer Epidemiol Biomarkers Prev 1996;5:621–5.
39. Ross RK, Pile MC, Coetzee GA, et al. Androgen metabolism and prostate cancer: establishing a model of genetic susceptibility. Cancer Res 1998;58:4497–4504.
40. Cohen P, Peehl DM, Rosenfeld RG. The IGF axis in the prostate. Horm Metab Res 1994;26:81–4.
41. Mantzoros CS, Tzonou A, Signorello LB, et al. Insulin-like growth factor 1 in relation to prostate cancer and benign prostatic hyperplasia. Br J Cancer 1997;76:1115–18.
42. Chan JM, Stampfer MJ, Giovannucci E, et al. Plasma insulin-like growth factor-I and prostate cancer risk: a prospective study. Science 1998;279:563–6.

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