Nutrition, Hormones and Prostate Cancer Risk: Results from the European Prospective Investigation into Cancer and Nutrition

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Abstract

Nutritional factors may influence the risk of developing prostate cancer, but understanding of this topic is poor. This chapter discusses research on this subject, mostly from the European Prospective Investigation into Cancer and Nutrition (EPIC), a cohort which includes 150,000 men recruited in the 1990s in eight European countries. So far the EPIC collaborators have published analyses of the relationship of prostate cancer risk with the intake of a range of foods and nutrients, and with blood-based markers of nutritional factors, on up to nearly 3,000 incident cases of prostate cancer. Most of the results of these analyses have been null, with no clear indication that the risk for prostate cancer is related to intakes of meat, fish, fruit, vegetables, fibre, fat or alcohol or with blood levels of fatty acids, carotenoids, tocopherols, B vitamins, vitamin D, or selenium. There is some evidence from EPIC that risk may be increased in men with a high intake of protein from dairy products, and analyses of hormone levels have shown that risk is higher in men with relatively high blood levels of insulin-like growth factor-I (IGF-I). More research is needed to better describe the relationships of prostate cancer risk with IGF-I and related hormones, and to better understand whether nutritional factors may influence risk through hormones or perhaps by other mechanisms.

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1 Introduction

The incidence of prostate cancer varies substantially between different countries, suggesting that there may be modifiable risk factors associated with lifestyle and environment. Currently, the only well-established risk factors for prostate cancer are age, family history, ethnic origin, family history and various genetic factors (Chan et al. 2005; Eeles et al. 2013). Over the last 30 years, many studies have investigated whether dietary and nutritional factors may influence risk, but the results of these studies have been generally inconsistent and inconclusive. Here, we summarise the results from a large prospective study in Europe, in which prostate cancer risk has been examined in relation to the intake of a range of foods and macronutrients, and to circulating biomarkers of nutritional factors. We also discuss the findings from EPIC and other studies on the relationship of prostate cancer risk with circulating concentrations of endogenous hormones.

2 Methods

The European Prospective Investigation into Cancer and Nutrition (EPIC) is a prospective study of approximately 500,000 men and women in ten European countries, recruited between 1992 and 2000. Full details of the study design have been published (Riboli 2002). Briefly, 150,000 of the participants recruited were men, living in eight countries: Denmark, Germany, Greece, Italy, the Netherlands, Spain, Sweden and the United Kingdom. At recruitment participants completed questionnaires on their diet and lifestyle, and most also provided blood samples from which serum, plasma, red blood cells and white blood cells were separated and stored at −80 °C or below. Participants have been followed to ascertain incident cancers and death; in most countries follow-up for cancer was through cancer registries, whereas for Germany and Greece follow-up for cancer was based on self-reported cancer diagnosis followed by confirmation through review of medical records.

For prostate cancer, analyses in EPIC have been planned to examine a range of hypotheses concerning the possible roles of nutritional, lifestyle and hormonal factors (Key et al. 2002). For potential risk factors assessed by questionnaire, such as dietary and lifestyle factors, analyses were conducted using Cox regression for the full cohort of men, with analyses stratified by recruitment centre (so that men

who developed prostate cancer were compared with men recruited in the same place in Europe, who had not developed prostate cancer during the same follow-up period). For risk factors measured in the blood samples, such as nutritional biomarkers and endogenous hormones, analyses were conducted using a nested case–control design, such that for each case one control was selected matched on study centre, age at blood collection and follow-up period; laboratory analyses were conducted blind to case–control status and were planned so that, in general, cases and their matched controls were assayed in the same batch, thus largely eliminating inter-assay variation from the case–control comparisons. Statistical analysis of these nested case–control studies was by conditional logistic regression on matched sets, so that men who developed prostate cancer were compared with men recruited in the same place in Europe, who had not developed prostate cancer during the same follow-up period.

3 Results

Analyses of the relationships of intake of major food groups with prostate cancer risk in EPIC have been generally null (Table 1); the only significant association observed was a positive association with intake of yogurt, with an odds ratio of 1.17 (1.04–1.31) for men with a high intake of yogurt compared to men with a low intake of yogurt (Allen et al. 2008a). Sub-group analyses showed no significant differences in these associations by stage or grade of disease at diagnosis.

For macronutrients, no association was observed between prostate cancer risk and intakes of total protein, fat, fibre or alcohol, but risk was higher in men with a high intake of dairy protein than in men with a low intake (odds ratio 1.22 (1.07–1.41); Allen et al. 2008a, Table 2). Sub-group analyses showed no significant differences in these associations by stage or grade of disease at diagnosis.

For nutritional biomarkers, no association was observed between prostate cancer risk and blood levels of carotenoids, B vitamins, vitamin D, selenium or genistein (Table 3). There was a positive association between prostate cancer risk and the percentage of palmitic acid in plasma phospholipids and an inverse association between prostate cancer risk and the percentage of stearic acid in plasma phospholipids (Crowe et al. 2008b), but no association with the branched chain fatty acid phytanic acid (Price et al. 2010, Table 3) or other fatty acids (results not shown). Sub-group analyses showed some evidence of heterogeneity for the association of fatty acids with risk by grade of disease, such that high levels of myristic acid and α-linolenic acid were associated with a higher risk for high grade disease but not for low grade disease (Crowe et al. 2008b). There was evidence of heterogeneity for the association of lycopene with risk by stage of disease, such that high levels of lycopene were associated with a lower risk for advanced disease but not for localised disease (Key et al. 2007). There was also some evidence of heterogeneity by stage for vitamin B12, such that high levels of vitamin B12 were associated with a higher risk for advanced disease but not for

Table 1 Food groups and prostate cancer risk (Allen et al. 2008a; Key et al. 2004)

Food group	Odds ratio (95 % CI) high versus low intake	Test for trend
Red meat	0.96 (0.82–1.12)	NS
Processed meat	0.93 (0.79–1.09)	NS
White fish	1.03 (0.90–1.18)	NS
Fatty fish	1.07 (0.95–1.21)	NS
Milk	1.01 (0.89–1.16)	NS
Cheese	1.04 (0.90–1.20)	NS
Yogurt	1.17 (1.04–1.31)	0.02
Fruit and vegetables	1.00 (0.79–1.26)	NS

CI confidence interval

Table 2 Macronutrients and prostate cancer risk (Allen et al. 2008a; Crowe et al. 2008a; Suzuki et al. 2009; Rohrmann et al. 2008)

Macronutrient	Odds ratio (95 % CI) high versus low intake	Test for trend
Protein	1.17 (0.96–1.44)	NS
Dairy protein	1.22 (1.07–1.41)	0.02
Fat	0.96 (0.84–1.09)	NS
Fibre	1.02 (0.87–1.19)	NS
Alcohol	0.88 (0.72–1.08)	NS

CI confidence interval

localised disease (Johansson et al. 2008). There was no evidence of heterogeneity by stage or grade for the other nutritional biomarkers.

For endogenous hormones, prostate cancer risk was not associated with serum concentrations of testosterone or free testosterone (Travis et al. 2007). Risk was higher in men with high levels of IGF-I than in men with low levels (odds ratio 1.69 (1.35–2.13); Fig. 1), with no evidence of heterogeneity by stage or grade of disease at diagnosis (Price et al. 2012), and prostate cancer risk was not associated with IGF binding protein 3 (Allen et al. 2007).

4 Discussion

In EPIC, we have examined a range of nutritional and hormonal factors in relation to the risk for prostate cancer. The strongest association we have observed is with IGF-I, and this finding is consistent with a pooled analysis of individual participant data from 12 prospective studies (including EPIC; Roddam et al. 2008). IGF-I is affected by nutritional factors such as energy and protein intake (Ketelslegers et al. 1995) and there is evidence that men with high intakes of animal protein (or

Table 3 Nutritional biomarkers and prostate cancer risk (Crowe et al. 2008b; Price et al. 2010; Key et al. 2007; Johansson et al. 2008; Travis et al. 2009; Allen et al. 2008b; Travis et al. 2012)

Biomarker	Odds ratio (95 % CI) high versus low concentration	Test for trend
Palmitic acid	1.47 (0.97–2.23)	0.03
Stearic acid	0.77 (0.56–1.06)	0.03
Phytanic acid	1.13 (0.76–1.68)	NS
β-carotene	0.92 (0.66–1.28)	NS
Lycopene	0.97 (0.70–1.34)	NS
Folate	1.30 (0.88–1.93)	NS
Vitamin B12	1.19 (0.87–1.63)	NS
Vitamin D	1.28 (0.88–1.88)	NS
Selenium	0.96 (0.70–1.31)	NS
Genistein	1.00 (0.79–1.27)	NS

CI confidence interval

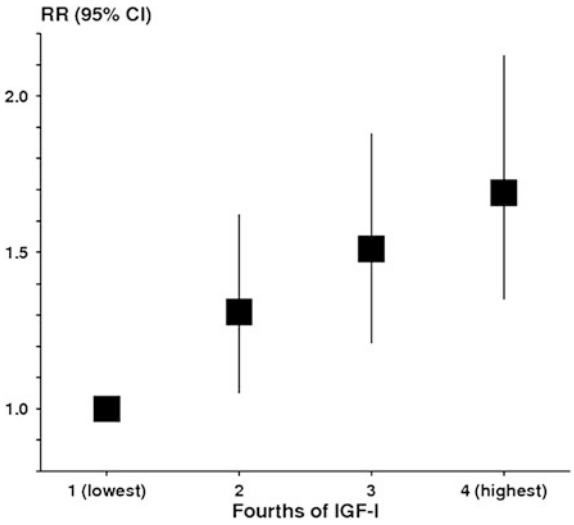

Fig. 1 Insulin-like growth factor-I and risk of prostate cancer in EPIC (figure adapted from results in Price et al. 2012)

particularly dairy protein) have relatively high circulating IGF-I (Giovannucci et al. 2003; Young et al. 2012), but more research is needed to better understand the nature of the effect of nutrition on IGF-I and on whether this effect is likely to have a material impact on the risk of prostate cancer (Key 2011). In EPIC, we observed a weak positive association of dairy protein with prostate cancer risk, and other studies have reported positive associations of risk with dairy foods (Qin et al. 2007; WCRF 2007), but this topic requires further study before firm conclusions can be drawn. In EPIC, we also observed that men with the lactase genotype

associated with lactase persistence have a higher intake of dairy products than men with the wild-type genotype for lactase (Travis et al. 2013), and the possibility that the lactase genotype is associated with prostate cancer risk should be examined in very large datasets.

We did not observe an association of endogenous sex hormones with prostate cancer risk, and this is consistent with the results of a pooled analysis of individual participant data from 18 prospective studies (Endogenous Hormones and Prostate cancer Collaborative Group 2008). These results indicate that androgen levels in the normal range are not associated with prostate cancer risk, but more research is needed to determine whether there may be a reduction in risk in men with particularly low androgen levels.

For the other nutritional factors examined in EPIC we have not found any strong associations. This is compatible with other studies worldwide, which have suggested that several nutritional factors may increase or decrease the risk for prostate cancer, but which have not established any definite effects (Chan et al. 2005; WCRF 2007). Further research is needed, because there may be real effects of moderate magnitude which could have major implications for disease prevention. Future studies need to collect data for very large numbers of men with prostate cancer and to collect detailed information on the characteristics of the tumour such as stage and grade, and on survival, to enable analyses of risk factors for aggressive prostate cancer (Wilson et al. 2012).

References

Allen NE, Appleby PN, Roddam AW, Tjønneland A, Johnsen NF, Overvad K et al (2008a) European Prospective Investigation into Cancer and Nutrition. Plasma selenium concentration and prostate cancer risk: results from the European Prospective Investigation into Cancer and Nutrition (EPIC). Am J Clin Nutr 88:1567–1575

Allen NE, Key TJ, Appleby PN, Travis RC, Roddam AW, Tjønneland A et al (2008b) Animal foods, protein, calcium and prostate cancer risk: the European Prospective Investigation into Cancer and Nutrition. Br J Cancer 98:1574–1581

Allen NE, Key TJ, Appleby PN, Travis RC, Roddam AW, Rinaldi S et al (2007) Serum insulin-like growth factor (IGF)-I and IGF-binding protein-3 concentrations and prostate cancer risk: results from the European Prospective Investigation into Cancer and Nutrition. Cancer Epidemiol Biomarkers Prev 16:1121–1127

Chan JM, Gann PH, Giovannucci EL (2005) Role of diet in prostate cancer development and progression. J Clin Oncol 23:8152–8160

Crowe FL, Key TJ, Appleby PN, Travis RC, Overvad K, Jakobsen MU et al (2008a) Dietary fat intake and risk of prostate cancer in the European Prospective Investigation into Cancer and Nutrition. Am J Clin Nutr 87:1405–1413

Crowe FL, Allen NE, Appleby PN, Overvad K, Aardestrup IV, Johnsen NF et al (2008b) Fatty acid composition of plasma phospholipids and risk of prostate cancer in a case-control analysis nested within the European Prospective Investigation into Cancer and Nutrition. Am J Clin Nutr 88:1353–1363

Eeles RA, Olama AA, Benlloch S, Saunders EJ, Leongamornlert DA, Tymrakiewicz M et al (2013) Identification of 23 new prostate cancer susceptibility loci using the iCOGS custom genotyping array. Nat Genet 45:385–391

Endogenous Hormones and Prostate Cancer Collaborative Group (2008) Roddam AW, Allen NE, Appleby P, Key TJ. Endogenous sex hormones and prostate cancer: a collaborative analysis of 18 prospective studies. J Natl Cancer Inst 100:170–183

Giovannucci E, Pollak M, Liu Y, Platz EA, Majeed N, Rimm EB et al (2003) Nutritional predictors of insulin-like growth factor I and their relationships to cancer in men. Cancer Epidemiol Biomarkers Prev 12:84–89

Johansson M, Appleby PN, Allen NE, Travis RC, Roddam AW, Egevad L et al (2008) Circulating concentrations of folate and vitamin B12 in relation to prostate cancer risk: results from the European Prospective Investigation into Cancer and Nutrition study. Cancer Epidemiol Biomarkers Prev 17:279–285

Ketelslegers JM, Maiter D, Maes M, Underwood LE, Thissen JP (1995) Nutritional regulation of insulin-like growth factor-I. Metabolism 44:50–57

Key TJ (2011) Diet, insulin-like growth factor-1 and cancer risk. Proc Nutr. Soc 70:1–4

Key TJ, Allen N, Appleby P, Overvad K, Tjønneland A, Miller A et al (2004) European Prospective Investigation into Cancer and Nutrition (EPIC). Fruits and vegetables and prostate cancer: no association among 1104 cases in a prospective study of 130544 men in the European Prospective Investigation into Cancer and Nutrition (EPIC). Int J Cancer 109:119–124

Key TJ, Appleby PN, Allen NE, Travis RC, Roddam AW, Jenab M et al (2007) Plasma carotenoids, retinol, and tocopherols and the risk of prostate cancer in the European Prospective Investigation into Cancer and Nutrition study. Am J Clin Nutr 86:672–681

Key TJ; EPIC Working Group on Prostate Cancer (2002) Prostate cancer: rates in Europe, dietary hypotheses, and plans for EPIC. IARC Sci Publ 156:197–200

Price AJ, Allen NE, Appleby PN, Crowe FL, Jenab M, Rinaldi S et al (2010) Plasma phytanic acid concentration and risk of prostate cancer: results from the European Prospective Investigation into Cancer and Nutrition. Am J Clin Nutr 91:1769–1776

Price AJ, Allen NE, Appleby PN, Crowe FL, Travis RC, Tipper SJ et al (2012) Insulin-like growth factor-I concentration and risk of prostate cancer: results from the European Prospective Investigation into Cancer and Nutrition. Cancer Epidemiol Biomarkers Prev 21:1531–1541

Riboli E, Hunt KJ, Slimani N, Ferrari P, Norat T, Fahey M et al (2002) European Prospective Investigation into Cancer and Nutrition (EPIC): study populations and data collection. Public Health Nutr 5:1113–1124

Roddam AW, Allen NE, Appleby P, Key TJ, Ferrucci L, Carter HB et al (2008) Insulin-like growth factors, their binding proteins, and prostate cancer risk: analysis of individual patient data from 12 prospective studies. Ann Intern Med 149:461–471

Rohrmann S, Linseisen J, Key TJ, Jensen MK, Overvad K, Johnsen NF et al (2008) Alcohol consumption and the risk for prostate cancer in the European Prospective Investigation into Cancer and Nutrition. Cancer Epidemiol Biomarkers Prev 17:1282–1287

Qin LQ, Xu JY, Wang PY, Tong J, Hoshi K (2007) Milk consumption is a risk factor for prostate cancer in Western countries: evidence from cohort studies. Asia Pac J Clin Nutr 16:467–476

Suzuki R, Allen NE, Key TJ, Appleby PN, Tjønneland A, Johnsen NF et al (2009) A prospective analysis of the association between dietary fiber intake and prostate cancer risk in EPIC. Int J Cancer 124:245–249

Travis RC, Allen NE, Appleby PN, Price A, Kaaks R, Chang-Claude J et al (2012) Prediagnostic concentrations of plasma genistein and prostate cancer risk in 1,605 men with prostate cancer and 1,697 matched control participants in EPIC. Cancer Causes Control 23:1163–1171

Travis RC, Appleby PN, Siddiq A, Allen NE, Kaaks R, Canzian F et al (2013) Genetic variation in the lactase gene, dairy product intake and risk for prostate cancer in the European prospective investigation into cancer and nutrition. Int J Cancer 132:1901–1910

Travis RC, Crowe FL, Allen NE, Appleby PN, Roddam AW, Tjønneland A et al (2009) Serum vitamin D and risk of prostate cancer in a case-control analysis nested within the European Prospective Investigation into Cancer and Nutrition (EPIC). Am J Epidemiol 169:1223–1232

Travis RC, Key TJ, Allen NE, Appleby PN, Roddam AW, Rinaldi S, Egevad L et al (2007) Serum androgens and prostate cancer among 643 cases and 643 controls in the European Prospective Investigation into Cancer and Nutrition. Int J Cancer 121:1331–1338

Wilson KM, Giovannucci EL, Mucci LA (2012) Lifestyle and dietary factors in the prevention of lethal prostate cancer. Asian J Androl 14:365–374

World Cancer Research Fund/American Institute for Cancer Research (2007) Food, nutrition, physical activity and the prevention of cancer: a global perspective, 1st edn. American Institute for Cancer Research, Washington

Young NJ, Metcalfe C, Gunnell D, Rowlands MA, Lane JA, Gilbert R et al (2012) A cross-sectional analysis of the association between diet and insulin-like growth factor (IGF)-I, IGF-II, IGF-binding protein (IGFBP)-2, and IGFBP-3 in men in the United Kingdom. Cancer Causes Control 23:907–917