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Fatherhood and incident prostate cancer in a prospective US cohort

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Background Fatherhood status has been hypothesized to affect prostate cancer risk but the current evidence is limited and contradictory.

Methods We prospectively evaluated the relationship between offspring number and the risk of prostate cancer in 161 823 men enrolled in the National Institues of Health – American Association of Retired Persons Diet and Health Study. Participants were aged 50–71 years without a cancer diagnosis at baseline in 1995. Analysing 8134 cases of prostate cancer, Cox regression was used to estimate the association between offspring number and prostate cancer incidence while accounting for socio-demographic and lifestyle characteristics.

Results When examining the entire cohort, there was no relationship between fatherhood and incident prostate cancer [hazard ratio (HR) 0.94, 95% confidence interval (CI) 0.86–1.02]. However, after stratifying for prostate cancer screening, prostate-specific antigen (PSA) unscreened childless men had a lower risk of prostate cancer (HR 0.73, 95% CI 0.58–0.91) compared with fathers due to the interaction between PSA screening and fatherhood (P for interaction < 0.01). A trend for the lower risk of prostate cancer among unscreened fathers compared with childless men was seen for low-grade prostate cancer (HR 0.78, 95% CI 0.61–1.01), high-grade prostate cancer (HR 0.62, 95% CI 0.37–1.04) and even fatal prostate cancer (HR 0.28, 95% CI 0.07–1.12). The number of children fathered was not related to prostate cancer ($P_{trend} = 0.17$). In addition, men's inability to sire female offspring showed a weak positive association with prostate cancer in the PSA unscreened study subjects.

Conclusions Our findings suggest fatherhood status and offspring gender is associated with a man's prostate cancer risk.

Keywords Fertility, prostatic neoplasms, fathers, sex ratio, family size

Introduction

Prostate cancer is the second leading cause of cancer-related death in the USA with an estimated 30 000 deaths annually and more than 200 000 cases diagnosed.[1] Age, family history and geographic and ethnic origins are all established risk factors for prostate cancer. Recently, several groups have explored whether fatherhood status is an independent risk factor for prostate cancer with varied results.[2–6]

A Swedish case–control study and a Danish cohort study both showed that childless men had a lower risk of prostate cancer compared with fathers, hypothesizing that androgen status may explain the relationship.[4,7] To explain the association, these groups suggested that some men with lower offspring numbers might have impaired fertility. Although male infertility is pathologically heterogeneous, in general there is a degree of testicular failure with impaired exocrine and endocrine functions. As prostate cancer is thought to be testosterone dependent, these groups suggested that men with fewer offspring would be at a lower androgen state and have a lower risk of prostate carcinogenesis.[8]

In contrast to the androgen hypothesis, the Danish cohort study and an Israeli cohort study both found that the risk of prostate cancer declined with increasing numbers of offspring among men with at least one child.[2,7] Moreover, the Israeli study showed that fathers who were unable to sire sons had an increased risk of prostate cancer, suggesting that the gender of offspring is also predictive of prostate cancer risk.[2] Other studies, and the most recent systematic review on the subject, have failed to show an association between fatherhood and prostate cancer risk.[5,9,10]

It is unknown whether the effects noted in the European studies are applicable in a US population, given the differences in prostate-specific antigen (PSA) screening and prostate cancer incidence that exist between the regions.[1,11,12] Given the prevalence of PSA screening in the USA and the attenuating effects PSA screening can have on the associations between genetic and dietary risk factors and prostate cancer, accounting for prostate cancer screening may be important when searching for links between prostate cancer and fatherhood.[13] To date, no large US study has examined the association between fatherhood status and the development of prostate cancer. In addition, individual pathologic data to establish separate cancer risks based on fatherhood status for low- and high-grade prostate cancer, as well as prostate-cancer-specific mortality are lacking.

Methods

Study population

In 1995–96, 3.5 million members of the AARP (formerly known as American Association of Retired Persons) aged 50–71 years living in one of six states (California, Florida, Louisiana, New Jersey, North Carolina and Pennsylvania) or two metropolitan areas (Atlanta, GA, and Detroit, MI) were mailed a questionnaire detailing medical history and lifestyle characteristics to initiate the NIH-AARP (National Institues of Health – American Association of Retired Persons) Diet and Health Study.[14] In all, 567 169 (16.2%) respondents satisfactorily completed the initial survey. In late 1996, a supplementary survey was mailed to those participants who had successfully completed the baseline survey and did not have prostate, breast or colon cancer at baseline. The additional questionnaire asked questions regarding number of offspring and prostate cancer screening history. The NIH-AARP Diet and Health study was reviewed and approved by the Special Studies Institutional Review Board of the US National Cancer Institute (NCI).

Among the 334 908 individuals who responded to the supplemental questionnaire, we excluded women ($n = 138\,057$), those who had the survey filled out by a proxy ($n = 3967$), men who had previously been diagnosed with cancer other than non-melanoma skin cancer ($n = 10\,040$), men with no follow-up ($n = 4$) and men with missing offspring data ($n = 15\,339$). In addition, men who had never been married ($n = 5678$) were excluded as reproductive opportunities of such men were difficult to assess. After these exclusions, there were a total of 161 823 men available for analysis.

Identification of incident prostate cancer cases and deaths

Cohort members were followed through 31 December 2003, with incident prostate cancer cases (International Classification of Diseases 9th version, rubric 185 or 10th version, rubric C61) identified by probabilistic linkage with a cancer registry database from the original eight states as well as Arizona, Nevada and Texas. Follow-up coverage was expanded to capture participants who moved from their original locations. Our case ascertainment method has been previously described, which demonstrated ~90% identification of incident cancers.[15] Low-grade prostate cancer was defined as Surveillance, Epidemiology and End Results grade 1 (well differentiated; Gleason grades 2–4) or grade 2 (moderately well differentiated; Gleason grades 5–7). High-grade prostate cancer was defined as grade 3 (poorly differentiated; Gleason grades 8–10) or grade 4 (undifferentiated or anaplastic). Deaths from prostate cancer as the underlying cause of death were assessed through linkage with the Social Security Administration Death Master File, the National Death Index Plus, cancer registry linkage, questionnaire responses and responses to other mailings, with a final evaluation 31 December 2005.

Assessment of offspring number

Information on offspring number was assessed by self-report. The survey asked: 'How many sons do you have, both living and deceased? Include blood relatives only' and 'How many daughters do you have, both living and deceased? Include blood relatives only.' Total offspring number was generated by summing the results of total sons and daughters. We collapsed those with four or more offspring into one category to ensure adequate statistical power.

Statistical analysis

Each participant accrued follow-up time from the date the supplementary questionnaire was returned until prostate cancer diagnosis, death, move out of registry ascertainment area or end of study period, 31 December 2003 (for incident prostate cancer analysis) or 31 December 2005 (for fatal prostate cancer analysis). Cox proportional hazards regression was used to estimate the relation between offspring number and prostate cancer incidence and mortality.[16] The proportional hazards assumption was assessed using log minus log plots and the Schoenfeld test and upheld for all analyses.[17]

Covariates were selected for inclusion in our a priori model that have been consistently shown in the literature to affect prostate cancer risk or offspring number. All multivariate models were adjusted for age, race, body mass index (BMI), marital status, educational attainment, smoking status, family history of prostate cancer and a personal history of digital rectal examination (DRE) or PSA prostate cancer screening. Tests for trend were performed by treating offspring number as a continuous variable in the Cox regression model after replacing each category (i.e. 0, 1, 2, 3, $\geqslant 4$) with the mean of the original variable. Effect modification was assessed using the likelihood ratio test by entering fatherhood along with the covariate of interest as well as the term for their product in the multivariable model. In addition, stratified analyses were also performed to judge effect modification. All statistical tests were two sided. STATA 10 (Statacorp, College Station, TX) was used for all analyses.

Results

During 1 093 365 person-years of follow up, 8134 men with incident prostate cancer were diagnosed. Of these, 6346 men had low-grade prostate cancer and 1322 men had high-grade disease. There were 296 prostate cancer deaths from 1996 until 2005. The mean age of participants was 63 years and the mean number of offspring was 2.6—1.3 sons and 1.3 daughters. Men with more offspring tended to be older, have lower educational attainment, have a higher BMI and be non-White. In addition, a history of prostate cancer screening (both DRE or PSA) was more common for fathers than childless men. For example, fathers were more likely to have undergone PSA screening within the 3 years prior to study enrolment (78.0%) compared with childless men (75.3%, Table 1).

In order to determine if fatherhood status affects a man's risk of prostate cancer, childless men were compared with men with at least one child. Men without children had a similar risk of prostate cancer to fathers [hazard ratio (HR) 0.94, 95% confidence interval (CI) 0.86–1.02]. However, after stratifying based on PSA screening history (*P* for interaction between fatherhood and PSA screening <0.01), there was a lower risk of prostate cancer among childless men compared with fathers in the unscreened population (HR 0.73, 95% CI 0.59–0.92; Table 2). Although fathering at least one child was associated with a man's diagnosis of prostate cancer, the number of children fathered by men did not affect a man's risk of prostate cancer ($P_{trend} = 0.17$, Table 2). An attempt to further examine reproductive intent and opportunity by stratifying based on current marital status did not materially change the conclusions.

The association between fatherhood and prostate cancer was next assessed after stratifying prostate cancer into low grade, high grade and fatal disease. A trend for lower risk of prostate cancer among PSA

Table 1 Distribution and characteristics of men according to number of offspring

	Offspring categories					
	0	1	2	3	⩾4	Total
Number of participants	12 909	16 102	52 288	42 336	38 188	161 823
Age (mean, years)	62.2	62.1	62.2	63.3	64.5	63.0
BMI (mean)	27.0	27.0	27.0	27.2	27.5	27.1
Smoking status (%)						
Never	31.5	29.5	31.7	30.7	28.7	30.5
Former	58.2	60.1	59.4	60.0	60.9	59.9
Current	10.3	10.5	8.9	9.3	10.4	9.6
Education (%)						
<12 years	4.8	4.8	4.1	4.7	6.8	5.0
High school/some college	45.1	48.4	45.0	46.7	50.1	47.0
College or higher	50.1	46.7	51.0	48.6	43.2	48.0
Race (%)						
White	94.7	94.0	95.4	95.3	93.6	94.8
Black	2.3	3.0	1.7	1.7	3.0	2.2
Other	3.0	3.0	2.9	3.0	3.4	3.1
First-degree relative with prostate cancer (Y, %)	8.8	8.7	8.9	9.0	9.1	8.9
Screening history (Y, %)						
PSA	75.3	75.2	78.3	79.1	77.6	77.8
DRE	84.3	84.3	86.5	87.2	85.4	86.0
Marital status (%)						
Currently married	82.3	84.7	89.7	90.4	89.7	88.8
Formerly married	17.8	15.3	10.3	9.6	10.3	11.2
Prostate cancer (total cases)						
Total	570	777	2466	2245	2076	8134
Low grade	443	607	1952	1718	1626	6346
High grade	91	125	378	390	338	1322
Fatal	18	32	81	79	86	296

Table 2 HRs and 95% CIs for prostate cancer according to the number of offspring

	All men			PSA screened men			PSA unscreened men		
	Cases (*n*)	HR (95% CI)	*P* value	Cases (*n*)	HR (95% CI)	*P* value	Cases (n)	HR (95% CI)	*P* value
Any children									
No	570	0.94 (0.86–1.02)	0.11	488	0.98 (0.90–1.08)	0.65	82	0.73 (0.59–0.92)	<0.01
One or more	7564	Reference		6300	Reference		1264	Reference	
Number of children									
No	570	0.92 (0.85–1.01)	0.12	488	0.96 (0.87–1.06)	0.46	82	0.77 (0.60–0.98)	0.03
One	777	1.01 (0.93–1.09)	0.90	635	1.00 (0.92–1.10)	0.95	142	1.01 (0.83–1.23)	0.90
Two	2466	0.95 (0.90–1.01)	0.11	2072	0.94 (0.88–1.00)	0.07	394	1.02 (0.88–1.18)	0.83
Three	2245	1.02 (0.96–1.08)	0.56	1866	1.00 (0.93–1.06)	0.92	379	1.14 (0.98–1.32)	0.08
Four or more	2076	Reference		1727	Reference		349	Reference	
Trend		1.01 (1.00–1.03)	0.06		1.01 (0.99–1.03)	0.25		1.03 (0.99–1.06)	0.17

Given the significant interaction between fatherhood and PSA screening ($P < 0.01$), stratified analyses by prostate cancer screening are listed. Cases signify the number of prostate cancer cases used in each analysis. All analyses adjusted for age, education, race, marital status, DRE screening, BMI, smoking status and family history of prostate cancer.

Table 3 HRs and 95% CIs for incident prostate cancer for childless men compared with fathers (reference)

Prostate cancer	All	Low grade	High grade	Death
All men				
Cases (*n*)	8134	6346	1322	296
HR	0.94 (0.86–1.02)	0.93 (0.85–1.03)	0.93 (0.76–1.15)	0.80 (0.50–1.28)
P-value	0.14	0.15	0.52	0.35
PSA screened men				
Cases (*n*)	6788	5365	1038	209
HR	0.98 (0.90–1.08)	0.97 (0.87–1.07)	1.01 (0.80–1.27)	1.04 (0.63–1.74)
P-value	0.72	0.51	0.96	0.87
PSA unscreened men				
Cases (*n*)	1346	981	284	87
HR	0.73 (0.59–0.92)	0.78 (0.61–1.01)	0.62 (0.37–1.04)	0.28 (0.07–1.12)
P-value	<0.01	0.06	0.07	0.07

Results are listed for all prostate cancers, low-grade prostate cancers, high-grade prostate cancers and fatal prostate cancers. Given the significant interaction between fatherhood and PSA screening ($P < 0.01$), stratified analyses by prostate cancer screening are listed. Cases signify the number of prostate cancer cases used in each analysis. All analyses adjusted for age, education, race, marital status, DRE screening, BMI, smoking status and family history of prostate cancer.

unscreened childless men compared with fathers was seen for low-grade prostate cancer (HR 0.78, 95% CI 0.61–1.01), high-grade prostate cancer (HR 0.62, 95% CI 0.37–1.04) and even fatal prostate cancer (HR 0.28, 95% CI 0.07–1.12, Table 3), despite the smaller number of cases available for these individual analyses.

The effect of offspring gender upon the relationship between fatherhood and prostate cancer was also studied among men with at least one child. Stratifying the analyses by number of children showed that as the number of total offspring rises, a father's inability to sire female offspring is associated with an increase in risk of prostate cancer in unscreened men (Table 4). However, there was no significant difference in the secondary gender ratio (sons : total offspring) between men who developed prostate cancer (51.4%, 95% CI 50.8–52.0) and those who did not (51.0%, 95% CI 50.8–51.1; $P = 0.18$).

Discussion

The current study found a lower risk of prostate cancer in childless men compared with fathers, whereas the risk of prostate cancer did not appear to vary with the total number of children sired. In addition, as the number of total offspring rose, a father's inability to sire female offspring was associated with an increased risk of prostate cancer. Interestingly, the association between fatherhood and prostate cancer is only seen in men who did

Table 4 HRs and 95% CIs for incident prostate cancer among fathers stratified by total number of offspring and ability to sire any sons or any daughters

		No daughters		No sons	
Number of offspring	**Cases (*n*)**	**HR (95% CI)**	***P*-value**	**HR (95% CI)**	***P*-value**
All men					
One or more	7564	1.02 (0.97–1.08)	0.43	1.00 (0.94–1.06)	0.91
Two or more	6787	1.04 (0.98–1.11)	0.20	0.98 (0.92–1.05)	0.59
Three or more	4321	1.07 (0.97–1.18)	0.20	1.04 (0.94–1.16)	0.44
Four or more	2076	0.94 (0.77–1.13)	0.49	1.07 (0.88–1.29)	0.51
PSA screened men					
One or more	6300	1.02 (0.96–1.08)	0.59	0.99 (0.93–1.06)	0.77
Two or more	5665	1.03 (0.95–1.10)	0.49	0.97 (0.90–1.05)	0.40
Three or more	3593	1.01 (0.91–1.13)	0.81	1.04 (0.93–1.17)	0.46
Four or more	1727	0.86 (0.69–1.07)	0.17	1.14 (0.93–1.40)	0.22
PSA unscreened men					
One or more	1264	1.07 (0.93–1.23)	0.35	1.01 (0.87–1.17)	0.88
Two or more	1122	1.16 (0.99–1.36)	0.07	0.98 (0.82–1.16)	0.80
Three or more	728	1.37 (1.09–1.72)	<0.01	0.99 (0.76–1.30)	0.95
Four or more	349	1.29 (0.83–2.01)	0.26	0.49 (0.24–0.99)	0.05

For the analyses examining daughters, the reference group is men who sired at least one daughter compared with men with no female offspring. For the analyses examining sons, the reference group is men who sired at least one son. Given the significant interaction between fatherhood and PSA screening ($P < 0.01$), stratified analyses by prostate cancer screening are listed. Cases signify the number of prostate cancer cases used in each analysis. All analyses adjusted for age, education, race, marital status, DRE screening, BMI, smoking status and family history of prostate cancer.

not undergo recent PSA screening. Thus, in an unscreened population, fatherhood does appear to be related to the diagnosis of prostate cancer.

Most of the current data linking prostate cancer risk to fatherhood status originates from European cancer registries. Using the Swedish cancer registry, Giwercman *et al*. showed that childless men were at a 17% decreased risk for prostate cancer compared with men with two or more offspring.[4] In a similar fashion, Jorgensen *et al*. showed that childless men had a 16% reduced risk of prostate cancer compared with fathers in Denmark.[3] Walsh and colleagues examined a man's reproductive potential without examining fatherhood status and found that men diagnosed with male factor infertility had an increased risk of high-grade prostate cancer.[18] It is also important to note that the cohort analysed by Walsh and colleagues included only men from couples evaluated for infertility and included younger men than the current report (>10 years on average).

In addition, the relationship between secondary sex ratio and prostate cancer varies between countries. Although Denmark and Sweden show no alteration in the gender of offspring fathered by men with prostate cancer,[3,4] Israeli men who develop prostate cancer have an impaired ability sire sons.[2] Harlap *et al*. postulated that such a finding was consistent with abnormalities on the Y chromosome, which could both harbour prostate cancer risk and impair a man's ability to produce male heirs. In contrast, the current study found that the inability to sire daughters increased a man's prostate cancer risk. Although the findings resulting from a subgroup analysis of PSA unscreened men may have resulted from chance, the inverse finding of a lower risk of prostate cancer in men unable to sire a male heir suggest that the X chromosome may be important for prostate cancer in the USA. Indeed, the X chromosome has been linked to prostate carcinogenesis containing the gene for the androgen receptor among other loci implicated in prostate cancer.[19–21]

The aetiology for the association between offspring number and prostate cancer risk remains speculative. Both the Swedish and Danish groups posit androgen status mediating the link between fatherhood and prostate cancer risk.[3,4] Indeed, the prostate is known to be a hormonally regulated with the thought that carcinogenesis is also androgen dependent.[8] Although a clear link between testosterone levels and prostate malignancy currently does not exist,[22] it is possible that androgen production or altered androgen sensitivity could provide the link between fatherhood status and prostate cancer. In the current report, some percentage of the group of childless men will be comprised of men that are unable to reproduce. Indeed, in the 2002 National Survey of Family

Growth, 75% of childless, married men of reproductive age in the USA reported a desire for offspring, suggesting that impaired fertility may play a role in preventing fatherhood status in some portion of this demographic group.[23] Although pathologically heterogeneous, male infertility usually consists of some degree of testicular failure that may result in a lower androgen status and thus lower prostate cancer risk. Indeed, infertile men may have lower testosterone levels than their fertile counterparts.[24] Alternatively, a link between fatherhood status and prostate cancer could result from a shared environmental exposure. Investigators have suggested that endocrine disrupting environmental contaminants may simultaneously increase malignancy risk and impair male fertility.[25–27]

An interaction between fatherhood and PSA screening was identified in our cohort. Indeed, our cohort had a relatively high rate of prostate cancer screening (77.6%); nearly as high as the treatment arms of the two recent randomized trials examining the mortality benefit for PSA screening (82.2–85%).[28,29] Although fatherhood was associated with the risk of prostate cancer in unscreened men, no relationship between offspring number and prostate cancer seemed to exist for men who underwent PSA screening at least once 3 years prior to study entry.

Indeed, PSA screening is known to attenuate the associations between genetic and dietary risk factors and prostate cancer.[13] Giovannucci argued convincingly about the contaminating effects that the current PSA screening practices may have on the incident prostate cancer endpoint when attempting to elucidate the actions of an associating factor.[30] In a screened population, a diagnosis of prostate cancer often occurs because a man happened to have a PSA screening test, which occurs equally in men both exposed and unexposed to the risk factor of interest. Thus in a screened group where both fathers and childless men are screened with PSA, screening-based prostate cancer ascertainment can overwhelm the naturally occurring prostate cancer that may be related to fatherhood status.

To our knowledge, this report represents the first exploration of fatherhood status and prostate cancer that incorporates PSA screening into the analysis. Although the Scandinavian studies are unlikely to be affected by PSA screening practices, due to its slower adoption in that region, Israeli and US studies could be strongly influenced by screening practices.[11,12] Any future examination of fatherhood status and offspring number should incorporate PSA screening practices.

Additional limitations warrant mention. Participants' reproductive intent, potential and ability of their partners were difficult to assess thus misclassification of exposure likely resulted across offspring categories. Men who desired no offspring and who could not sire children were jointly classified as childless. As we interpreted fecundity as a surrogate for paternity potential, such differential misclassification would likely result in regression to the null, which would be expected to lead to an underestimate of the association between fatherhood and prostate cancer found in this study. It is also conceivable that the relationship between fatherhood and cancer in unscreened men may have resulted from unmeasured confounding or chance alone.[31] Offspring number was self-reported and could be inaccurate; however, other studies have established the accuracy of self-reported reproductive histories.[32–34] Although we found no evidence of an effect modification by age, it is possible that the relationship between prostate cancer and offspring number could be different for men younger than those eligible for AARP membership. Given prostate cancer's slow growth rate, our follow-up period was relatively short. Moreover, as only 16% of those AARP members who were invited to participate ultimately returned questionnaires, volunteer bias could affect results. In addition, we were unable to account for parental age and birth order in our analysis, all of which are thought to affect the secondary sex ratio to some degree.[35–37] Importantly, there was significant effect modification between fatherhood and PSA screening with the reduced risk associated with being childless restricted to men who had no history of PSA screening. Although information regarding PSA screening 3 years prior to cohort recruitment was available, less is known about prostate cancer screening subsequently. Finally, the analyses examining high-grade and fatal prostate cancer involved few cases and have wide CIs that require careful intepretation.

Nevertheless, our study is the largest US cohort study to examine the relationship between fatherhood and prostate cancer. Our prospective design avoids the recall and selection bias inherent in case–control studies. Our high statistical power, with more than 8000 prostate cancers, and the ability to control for potential confounding demographic and lifestyle factors further strengthened our analysis.

In summary, we observed that childless men had a lower risk of prostate cancer among PSA unscreened men. Our findings suggest fatherhood status and offspring gender is associated with a man's prostate cancer risk. More studies are warranted to examine the correlation between men's reproductive history and prostate cancer risk.

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Conflict of interest: M.E. is an advisor to Quanterix Corporation.

KEY MESSAGES

- The current report represents the largest assessment in the USA examining the relationship between fatherhood and prostate cancer.
- In the entire cohort, there was no definitive relationship between prostate cancer and offspring number.
- In PSA unscreened men, however, childless men had a lower risk of prostate cancer compared with fathers.
- Our findings also suggest that offspring gender is associated with a man's prostate cancer risk.
- Limitations of the current report necessitate future studies to examine if the relationship between fatherhood and prostate cancer is a causal one or represents common risk factors.

References

[1] Jemal A, Siegel R, Ward E *et al*. Cancer statistics, 2008. *CA: a cancer journal for clinicians* 2008;**58:**71–96.

[2] Harlap S, Paltiel O, Friedlander Y *et al*. Prostate cancer in fathers with fewer male offspring: the Jerusalem Perinatal Study cohort. *J Nat Cancer Ins* 2007;**99:**77–81.

[3] Jorgensen KT, Pedersen BV, Johansen C, Frisch M. Fatherhood status and prostate cancer risk. *Cancer* 2008; **112:**919–23.

[4] Giwercman A, Richiardi L, Kaijser M, Ekbom A, Akre O. Reduced risk of prostate cancer in men who are childless as compared to those who have fathered a child: a population based case–control study. *Int J Cancer* 2005;**115:** 994–97.

[5] Dennis LK, Dawson DV. Meta-analysis of measures of sexual activity and prostate cancer. *Epidemiology* 2002; **13:**72–79.

[6] Negri E, Talamini R, Bosetti C, Montella M, Franceschi S, La Vecchia C. Risk of prostate cancer in men who are childless. *Int J Cancer* 2006;**118:**786–87.

[7] Jorgensen KT, Frisch M. Linking fatherhood to prostate cancer risk. *Future Oncology* 2008;**4:**137–40.

[8] Platz EA, Giovannucci E. The epidemiology of sex steroid hormones and their signaling and metabolic pathways in the etiology of prostate cancer. *J Steroid Biochem Mol Biol* 2004;**92:**237–53.

[9] Severson RK, Nomura AM, Grove JS, Stemmermann GN. A prospective study of demographics, diet, and prostate cancer among men of Japanese ancestry in Hawaii. *Cancer Res* 1989;**49:**1857–60.

[10] Hayes RB, Pottern LM, Strickler H *et al*. Sexual behaviour, STDs and risks for prostate cancer. *Brit J Cancer* 2000;**82:** 718–25.

[11] Jonler M, Eddy B, Poulsen J. Prostate-specific antigen testing in general practice: a survey among 325 general practitioners in Denmark. *Scand J Urol Nephrol* 2005;**39:** 214–18.

[12] Kvale R, Auvinen A, Adami HO *et al*. Interpreting trends in prostate cancer incidence and mortality in the five Nordic countries. *J Nat Cancer Ins* 2007;**99:** 1881–87.

[13] Giovannucci E, Liu Y, Platz EA, Stampfer MJ, Willett WC. Risk factors for prostate cancer incidence and progression in the health professionals follow-up study. *Int J Cancer* 2007;**121:**1571–78.

[14] Schatzkin A, Subar AF, Thompson FE *et al*. Design and serendipity in establishing a large cohort with wide dietary intake distributions: the National Institutes of Health-American Association of Retired Persons Diet and Health Study. *Am J Epidemiol* 2001; **154:**1119–25.

[15] Michaud DS, Midthune D, Hermansen S *et al*. Comparison of cancer registry case ascertainment with SEER estimates and self-reporting in a subset of the NIH-AARP Diet and Health Study. *J Registry Manage* 2005;**32:**70–75.

[16] Cox DR. Regression models and life tables [with discussion]. *J Royal Statis Soc* 1972;**34:**187–220.

[17] Vittinghoff E, Glidden DV, Shiboski SC, McCulloch CE. *Regression Methods in Biostatistics: Linear, Logistic, Survival, and Repeated Measures Models*. New York: Springer, 2005.

[18] Walsh TJ, Schembri M, Turek PJ *et al*. Increased risk of high-grade prostate cancer among infertile men. *Cancer* May 1;**116**:2140–47.

[19] Spatz A, Borg C, Feunteun J. X-chromosome genetics and human cancer. *Nat Rev* 2004;**4:**617–29.

[20] Visakorpi T, Hyytinen E, Koivisto P *et al*. *In vivo* amplification of the androgen receptor gene and progression of human prostate cancer. *Nat Gene* 1995;**9:**401–6.

[21] Monroe KR, Yu MC, Kolonel LN *et al*. Evidence of an X-linked or recessive genetic component to prostate cancer risk. *Nat Med* 1995;**1:**827–29.

[22] Roddam AW, Allen NE, Appleby P, Key TJ. Endogenous sex hormones and prostate cancer: a collaborative analysis of 18 prospective studies. *J Nat Cancer Ins* 2008;**100:** 170–83.

[23] Martinez GM, Chandra A, Abma JC, Jones J, Mosher WD. Fertility, contraception, and fatherhood: data on men and women from cycle 6 (2002) of the 2002 National Survey of Family Growth. *Vital Health Stat* 2006;**23:**1–142.

[24] Andersson AM, Jorgensen N, Frydelund-Larsen L, Rajpert-De Meyts E, Skakkebaek NE. Impaired Leydig cell function in infertile men: a study of 357 idiopathic infertile men and 318 proven fertile controls. *J Clin Endocrinol Meta* 2004;**89:**3161–67.

[25] Skakkebaek NE, Rajpert-De Meyts E, Main KM. Testicular dysgenesis syndrome: an increasingly common developmental disorder with environmental aspects. *Hum Rep* 2001;**16:**972–78.

[26] Xu X, Dailey AB, Talbott EO, Ilacqua VA, Kearney G, Asal NR. Associations of serum concentrations of organochlorine pesticides with breast cancer and prostate cancer in U.S. adults. *Environ Health Perspect* 2010;**118:**60–66.

[27] Joensen UN, Bossi R, Leffers H, Jensen AA, Skakkebaek NE, Jorgensen N. Do perfluoroalkyl compounds impair human semen quality? *Environ Health Perspect* 2009;**117:**923–27.

[28] Andriole GL, Grubb RL, 3rd, Buys SS *et al*. Mortality results from a randomized prostate-cancer screening trial. *New Eng J Med* 2009;**360:**1310–19.

[29] Schroder FH, Hugosson J, Roobol MJ *et al*. Screening and prostate-cancer mortality in a randomized European study. *New Eng J Med* 2009;**360:**1320–28.

[30] Giovannucci E. Does prostate-specific antigen screening influence the results of studies of tomatoes, lycopene, and prostate cancer risk? *J Nat Cancer Inst* 2007;**99:** 1060–62.

[31] Kravdal O. Is the relationship between childbearing and cancer incidence due to biology or lifestyle? Examples of the importance of using data on men. *Int J Epidemiol* 1995;**24:**477–84.

[32] Harlow SD, Linet MS. Agreement between questionnaire data and medical records. The evidence for accuracy of recall. *Am J Epidemiol* 1989;**129:**233–48.

[33] Nitsch D, Morton S, DeStavola BL, Clark H, Leon DA. How good is probabilistic record linkage to reconstruct reproductive histories? Results from the Aberdeen Children of the 1950s study. *BMC Med Res Methodol* 2006;**6:**15.

[34] Paganini-Hill A, Ross RK. Reliability of recall of drug usage and other health-related information. *Am J Epidemiol* 1982;**116:**114–22.

[35] Erickson JD. The secondary sex ratio in the United States 1969–71: association with race, parental ages, birth order, paternal education and legitimacy. *Ann Human Genet* 1976;**40:**205–12.

[36] Jacobsen R, Moller H, Mouritsen A. Natural variation in the human sex ratio. *Human Rep* 1999;**14:**3120–25.

[37] James WH. The human sex ratio. Part 1: a review of the literature. *Human Biol* 1987;**59:**721–52.