Late Fetal Death in Offspring and Subsequent Incidence of Prostate Cancer in Fathers: The Jerusalem Perinatal Study Cohort

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BACKGROUND. Little is known of the causes of prostate cancer and few previous studies have investigated men's reproductive histories in relation to this disease. We sought to determine whether risk of prostate cancer was altered in men who had fathered stillborn offspring.

METHODS. We studied the incidence of prostate cancer (N = 252) in a cohort of 15,268 fathers followed for 28–41 years from the birth of a live offspring, whose wives participated in one of two separate surveys of outcomes of previous births. Proportional hazards models were used to estimate relative risks (RR) associated with previous stillbirths, controlling for changes in incidence over time, social and occupational factors.

RESULTS. The 543 men with one or more stillborn offspring experienced an increased risk of prostate cancer (adjusted RR = 1.87, 95% confidence interval = 1.17–3.00, $P = 0.0095$), compared to men without stillbirths. With one reported stillbirth, the RR was 1.68 (0.99–2.84); with two or more, the RR was 3.29 (1.22–8.88). Results were consistent in men whose wives were interviewed in 1965–1968 and 1974–1976. In 100 fathers with no male offspring and at least one stillbirth the RR was 4.04 (1.87–8.71, $P = 0.0004$).

CONCLUSIONS. These findings should be considered hypothesis-generating and require confirmation in other studies. They suggest that stillbirth and prostate cancer may have shared environmental causes; alternatively, genetic susceptibility to prostate cancer might increase the risk of a stillbirth in offspring. *Prostate 67: 989–998, 2007.*

KEY WORDS: **prostate cancer; stillbirth; cohort studies; review**

INTRODUCTION

We recently reported an increased risk of prostate cancer in Israeli men lacking sons [1]. The relative risks associated with absence of sons were 1.3, 1.4 or 1.6 in men with 1, 2 or 3+ offspring, respectively ($P < 0.0001$). Possible explanations might be reduced ability to conceive male offspring, early loss of male embryos or selective loss of males through spontaneous abortions or fetal deaths. Any of these might derive from an abnormal X or Y chromosome, incompatibility between a man's Y and one of his wife's X chromosomes, or mutations of an autosomal gene. To cast further light on this subject in our population, we aimed to assess the

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incidence of prostate cancer in relation to a history of stillbirth. To our knowledge, there is no previous research on this specific topic.

METHODS

Study Population

This study is based on surveillance of cancer incidence and vital status in a cohort of families known as the Jerusalem Perinatal Study; currently these are nuclear families with middle-aged and elderly parents and their young adult offspring. During 1964–1976, all 92,408 births to residents of Western (Israeli) Jerusalem were surveyed. Items abstracted from the birth certificate included demographic information on the parents and both grandfathers; these were supplemented with data abstracted from medical records in obstetric departments, interviews with mothers and surveillance of pediatric inpatient departments. The methods and characteristics of the Jerusalem Perinatal Study population have been described [2–4]. This study was approved by the institutional review boards at Hadassah—Hebrew University Medical Center, Jerusalem, and Columbia University Medical Center, New York, and was exempted from the requirement for informed consent.

The cohort was linked with Israel's Population Registry in order to trace offspring and parents, i.e. verify identity numbers (IDs) and obtain either a current address or a date of death. The IDs of traced fathers were linked to Israel's Cancer Registry in 2005. This registry is considered to be fairly complete [5], 95% of all registered solid tumors and more than 94% of prostate tumors being histologically verified [6]. Diagnoses, topography and morphology are recorded according to the International Classification of Diseases for Oncology (ICD-O[7]). For this study, we took fully invasive first primary prostate carcinoma in fathers (topography code = C61).

In 1965–1968, 9,827 mothers of 11,647 offspring were interviewed in antenatal clinics, being questioned, inter alia, about the outcome of their previous pregnancies. Because this interview was done in the free municipal clinics, it bypassed many of the more affluent women, who chose to use private gynecologists, and a few of the poorest, who neglected antenatal care altogether. It also bypassed some women at high risk for complicated pregnancies (e.g. under care for infertility or previous miscarriage) who were receiving antenatal care in special clinics. This first sub-cohort with interviews covered 6.5% of the area's births in 1965, 67.5% in 1966 and 64.7% and 50.5% of births in 1967 and 1968, respectively. The 9,827 respondents included 7,415 (75.5%) with at least one previous pregnancy; of these, 38.8% claimed 1–11 previous miscarriages and 4.3% reported 1–4 stillbirths; some 9.5% had 1–11 induced abortions.

A second sub-cohort was more broadly representative of all births. It included 98% of mothers delivering in the area's three largest hospitals between November 1974 and December 1976, capturing 91% of all births in the area. The 15,224 mothers, interviewed 1–3 days after giving birth to 16,909 offspring, included 11,342 (74.5%) with at least one previous pregnancy, 30.2% claiming 1–9 previous miscarriages and 2.7% reporting 1–6 previous stillbirths; 15.3% had 1–12 induced abortions. We used the data from the latest interview in women who answered each questionnaire in more than one pregnancy.

Data Analysis

We used SAS® Version 9.1 to analyze the data. In preliminary analyses we calculated incidence rates based on person-years of observation. Then, we used methods of survival analysis to assess differences in time to disease incidence between the study groups. Cox proportional hazards regression models were used to control for covariates. Assumptions of proportionality were verified by inspecting ''log-negative-log'' plots [8] and by testing each variable as a time-dependent product of its value (0, 1) with length of follow-up. Each man's follow-up was started 9 months prior to the birth of the first of his live offspring observed in the Jerusalem Perinatal Study and ended at his death or his being diagnosed with invasive cancer at any site. Follow-up for survivors was censored on December 31, 2004. Potential covariates included the man's age at the start of follow-up, expressed as deviations from the mean (age 28); year of his birth (5-year groups); social class (an ordinal scale [3] based on occupation at the most recently observed birth, coded from 1 (well-off) to 6 (poor)); and a series of dichotomies coded 1 (present) or 0 (absent) representing categories of years of education (0–4, 5–8, 9–12, 13+, unknown); his wife's job (three categories of employment outside the home vs. housewives); a man's occupation as a rabbi or student in a Talmudic academy at any time (vs. never) and ethnic origin based on the man's father's place of birth (Israel, other Western Asia, North Africa, Europe; included in the latter were the Americas, sub-Saharan Africa, Australia and New Zealand). Variables were included in the models if they were related to the incidence of prostate cancer and to stillbirths ($P < 0.05$) and/or if their addition or removal altered, by at least 10%, the estimate of relative risk of prostate cancer associated with stillbirth. Other variables tested, of which none were retained in the models, were the man's religion (Muslim vs. Jewish), one or more of his offspring with low birthweight (<2.5 kg vs. none), high

birthweight (4.0+ kg vs. none), major birth defect (any vs. none), minor birth defect (any vs. none), his wife's level of education and her parity (number of births) at the start of follow-up. In order to take into account the sudden increase in diagnoses of prostate cancer that followed the introduction of prostate specific antigen (PSA) in 1991, we introduced two time-dependent dichotomies to control for the excess risk that applied to the passage of time through the specific calendar years, 1991–1995 and 1996–2004; the reference group for these represented time prior to 1991.

We analyzed the data derived from the wives' interviews in 1965–1968 separately from those from 1974 to 1976. Results were similar, however, so that we combined the two data sets to present some results; if so, we used the responses from the latest interview, for men whose wives had contributed to both sub-cohorts.

RESULTS

Tracing and Derivation of Numbers

We traced 98% of the 91,467 live born offspring in Israel's Population Registry and through them found 38,995 (95.7%) of their fathers. Tracing was more complete for Jewish fathers (97%) than for Muslims (87%) or Christians (36%), many of the latter being diplomats or foreign students. Similarly, tracing was better for men born in Israel (97%), Western Asia (97%) or North Africa (97%) than for those born in Europe, etc. (89%) who also included more students. After linking the 38,995 traced fathers' identity numbers to Israel's Cancer registry, we identified 8,584 men with malignancies. We deleted 58 diagnosed before the estimated date of conception of the man's first observed offspring, and three additional men with unknown dates of death (0.05% of 6,324 deaths), leaving a base cohort of 38,934. Of these, 8,526 developed any malignant disease during the 27–40 years of follow-up, including 712 who developed prostate cancer. The median age at diagnosis of prostate cancer was 68 (range = 42–87) and the median length of follow-up from the offspring's birth to the date of diagnosis was 31 years (range = 7–41).

For offspring whose mothers participated in the first interview, we traced the fathers of 93%; for the second interview, 95%. After excluding those whose wives reported no previous births, there were 15,268 men available for study, including 6,520 whose wives participated in the first interview and 10,040 with data from the second. There were 252 men who developed prostate cancer in the 15,268 whose wives were interviewed and 460 prostate cancer cases in the 23,666 without interviews. There were no significant differences in the incidence of prostate cancer between the men with and without interviewed wives, after adjusting for demographic differences: the adjusted relative risk (RR) of prostate cancer in the group with interviews was 0.93 (0.80–1.09, $P = 0.386$), compared with those without interviews. For the men whose wives participated in the first and second interviews, the adjusted RRs were 0.83 (0.69–1.01, $P = 0.056$) and 1.11 (0.90–1.36, $P = 0.334$), respectively, compared to men whose wives did not participate.

Characteristics of Men With and Without Stillborn Offspring

In the 15,268 men with interviews, there were 543 (3.6%) whose wives reported one or more stillbirths; this proportion was 5.1% from the earlier interview and 2.9% from the more recent one. Table I compares the characteristics of these men, compared with those with no stillbirths. Trends from the two separate interviews were similar and the table shows the combined data. Men with stillborn offspring were more likely to be older at the start of follow-up, with an earlier year of birth; they were of lower social class and were less educated. There were also some differences between ethnic groups, men with stillbirths more often being Muslims or immigrants from Islamic countries; they were less likely than those without stillbirths to be rabbis or Talmud students.

Main Findings

Table II estimates the relative risk of prostate cancer in men whose wives had stillbirths, comparing the age-adjusted risk with estimates adjusted for other variables. In the data from both interviews combined, there was a 71% increase in the age-adjusted risk of prostate cancer associated with stillbirths; this estimate was increased slightly (to 87%) by adjusting for confounders. There was evidence suggesting a ''dose–response'' relationship with the number of stillbirths. Results were consistent in the two sub-cohorts, both showing a statistically significant excess risk associated with any stillbirth or with multiple stillbirths and both showing an increase in risk associated with a higher number of stillbirths. Not shown in the table, we observed a consistently increased risk of prostate cancer associated with stillbirths, whether in men diagnosed before age 65 (1.63, 0.76–3.51) or diagnosed at later ages (2.16, 1.19–3.95) or whether the men were born before 1940 (1.90, 1.15–3.13) or born more recently (1.76, 0.43–7.29).

Secondary Analyses

Table III estimates the combined effects of lack of male offspring and history of stillbirth. There was a

TABLE I. Percent Distribution of Characteristics of Men Whose Wives did or did not Report Stillbirths, by Selected Variables

	Stillbirths		
	None	One or more	*P*
Number of men	14,725	543	
Percent	100.0	100.0	
Age at start of follow-up			
<25	26.8	14.9	
25–34	55.0	50.6	<0.0001
35–44	15.5	27.6	
45+	2.6	6.8	
Cohort year of birth			
<1925	4.8	14.0	
1925–1929	7.5	14.2	
1930–1934	14.9	20.4	
1935–1939	20.8	18.2	<0.0001
1940–1944	20.3	17.1	
1945–1949	23.0	11.6	
1950+	8.7	4.4	
Social class			
(high) 1	14.4	8.7	
2	20.5	11.6	
3	17.7	15.5	<0.0001
4	18.7	22.8	
5	13.7	16.2	
(low) 6	15.1	25.2	
Years of education			
13+	33.7	18.2	
9–12	32.9	28.0	<0.0001
5–8	24.6	32.0	
0–4	6.0	16.2	
Unknown	2.9	5.5	
Wife's occupational social class			
(High) 1	16.5	7.7	
(Medium) 2	13.3	9.9	<0.0001
(Low) 3	6.5	9.2	
Housewives	63.7	73.1	
Religion			
Muslim	1.0	3.1	<0.0001
Christian	0.1	—	
Jewish	98.9	96.9	
Place of birth			
Israel	15.5	12.0	
Other West Asia	32.7	44.0	<0.0001
North Africa	22.4	25.8	
Europe, etc.	29.4	18.2	
Rabbis/Talmudic students			
Yes	15.2	7.7	<0.0001
No	84.8	92.3	
Male offspring			
Any	82.2	81.4	0.604
None	17.8	18.6	

statistically significant four-fold increase in risk of prostate cancer in men with no live male offspring whose wives had stillbirths. Lack of male offspring was also a significant risk factor for prostate cancer when not associated with stillbirth. Men with male offspring and a history of stillbirth showed a raised risk of prostate cancer, though this was more likely to be due to chance. The risk associated with the combination of stillbirth and lack of male offspring was somewhat greater than would be expected from the independent effects of these two variables; although this interaction was not statistically significant at the 5% level ($X^2 = 3.456$, $P = 0.063$), it was observed in the data from both first and second interviews (data not shown).

In the second interview, the mothers were questioned about smoking and 49.3% reported that their husbands had ever smoked. Although a history of stillbirth was more prevalent in wives of smokers (3.3% vs. 2.5% in non-smokers' wives, $P = 0.02$), men who had ever smoked showed no significantly altered risk of prostate cancer (adjusted RR = 0.80, 0.56–1.16, $P = 0.241$) compared with men who never smoked. Therefore, smoking did not explain the association of prostate cancer with stillbirth.

DISCUSSION

This study shows an association of prostate cancer with a history of fathering a stillborn offspring. This association is unlikely to be due to chance. It is consistent in the two sub-cohorts that rely on data from two different interviews, done a decade apart. It shows some evidence for a ''dose–response'' effect with the number of stillbirths. The association is not explained by smoking or those other potential confounders that we could adjust for, i.e. social class, education, ethnic group, occupation as a rabbi or student in a Talmud academy at any time, cohort year of birth or the increase in incidence that occurred after 1991, when testing with PSA came into use. Other, undetected, causes of confounding cannot be excluded, however. One possible explanation is that stillbirth might be a ''risk marker'' for an environmental cause of prostate cancer in men that also, independently, might cause stillbirth in women. On the other hand, the outcome in offspring might be the more direct consequence of damage to the male reproductive system. Prostate cancer has been speculatively related to smoking [9,10], cadmium [11–13], lead and other heavy metals [14]; disturbed metabolism or transport of zinc [15], polycyclic aromatic hydrocarbons [16], diesel fumes or fuel [17], PCBs [18,19], dioxin-related compounds [20–23] and exposure to herbicides, pesticides and related chemicals during manufacture, application [20] or occupations such as farming [24,25]. The incidence of prostate

TABLE II. Numbers of Men With and Without Prostate Cancer, Relative Risks (RR) and 95% Confidence Intervals (CI) by History of Stillbirth, Numbers of Stillbirths and Date of Wife's Interview

	Prostate cancer		Age-adjusted			Adjusted further[a]		
	No	Yes	RR	95% CI	*P*	RR	95% CI	*P*
Data from both sub-cohorts combined								
History of stillbirths								
No	14,492	233	1	Ref.		1	Ref.	
Yes	524	19	1.71	1.07–2.73	0.0250	1.87	1.17–3.00	0.0095
Number of stillbirths								
1	468	15	1.53	0.91–2.58	0.1110	1.68	0.99–2.84	0.0543
2+	56	4	3.04	1.13–8.18	0.0278	3.29	1.22–8.88	0.0186
Data from wives interviewed in 1965–1968								
History of stillbirths								
No	6,050	141	1	Ref.		1	Ref.	
Yes	315	14	1.80	1.04–3.12	0.0364	1.90	1.16–2.36	0.0237
Number of stillbirths								
1	274	11	1.63	0.88–3.01	0.1217	1.72	0.93–3.20	0.0856
2+	41	3	2.92	0.95–9.35	0.0625	3.04	0.97–9.57	0.0575
Data from wives interviewed in 1974–1976								
History of stillbirths								
No	9,616	111	1	Ref.		1	Ref.	
Yes	282	11	2.18	1.17–4.07	0.0144	1.76	1.13–2.74	0.0069
Number of stillbirths								
1	258	7	1.58	0.74–3.41	0.2411	1.72	0.80–3.72	0.1671
2+	24	4	6.54	2.40–17.8	0.0002	7.49	2.72–20.7	<0.0001

[a]Adjusted for age (continuous), calendar year (1996+, 1991–1995 vs. earlier), man's year of birth (1950+, 1945–1949, 1940–1944 vs. earlier), years of education (13+ vs. others), the man's occupational social class (continuous), wife's social class (highest group, vs. all others), North African origin (vs. all other ethnic groups and rabbis and students in Talmud academies (ever vs. never).

cancer, and/or mortality from it, have also been seen to be increased in workers exposed to electromagnetic fields [26], ionizing radiation [27–29], metal dust or metalworking fluids [30,31] and other hazardous environments [32,33]. For some of these exposures there is evidence of a window of susceptibility at a young age and a latency of 25 years or more before the risk of prostate cancer is manifest [34] whereas little or no risk may be apparent after short term follow-up [35].

Stillbirths have become increasingly rare during the past few decades [36,37]. Recent reviews of their epidemiology and causes have generally ignored the contribution of fathers [38–40]. Maternal factors associated with stillbirths include the extremes of age [40–42] and parity [43], smoking [44], alcohol drinking [45], caffeine [46], obesity or excess weight gain [47–49], and various medical conditions [39,40,50–53]. Numerous other risk factors attributed to mothers seem more likely to reflect health characteristics of fathers; and many of these would be relevant to prostate cancer. Apart from smoking, alcohol and illicit drugs [54] these might include sexually transmitted and other infections [40,55,56], variables associated with domestic violence [57], lower social class [58], race or ethnic groups associated with poverty [59,60], starvation (famine) [61]; exposure to heavy metals including mercury [62], cadmium [63], arsenic [64,65] and lead [66]; or other types of environmental pollution [67–73]. In spite of a widespread belief that stillbirths are linked to environmental toxins, however, many studies focused on individual pollutants have derived negative results and specific risks are hard to verify.

A few studies have directly investigated paternal risk factors for stillbirths but their conclusions have often been controversial. One longstanding controversy surrounds the reproductive health effects of men's exposures to dioxin-related compounds during military service in Vietnam [74] that finds echoes in concerns about effects on veterans from the first Gulf war [75]. Some evidence from a study of Vietnam veterans suggested an excess of stillbirths in their offspring [76], and stillbirths have been observed in offspring of male rats experimentally exposed to dioxins and related compounds [77]. Another controversy concerns the reproductive consequences of

TABLE III. Numbers of Men With and Without Prostate Cancer, Adjusted* Relative Risks (RR) and 95% Confidence Limits (CL), by Numbers of Male Offspring and Numbers of Stillbirths

	Number of stillbirths		
Number of male offspring	One or more	None	Total[b]
None			
Prostate cancer			
Yes	7	64	71
No	93	2,544	2,637
RR	4.04	1.59	1.65
95% CI	1.87–8.71	1.19–2.14	1.24–2.19
P	0.0004	0.0020	0.0005
One or more			
Prostate cancer			
Yes	12	169	181
No	431	11,948	12,379
RR	1.62	1	1
95% CI	0.90–2.92	Ref.	Ref.
P	0.1073	—	—
Total[a]			
Prostate cancer			
Yes	19	233	252
No	524	14,492	15,016
RR	1.87	1	—
95% CI	1.17–3.00	Ref.	—
P	0.0095	—	—

*Adjusted for age (continuous), calendar year (1996+, 1991–1995 vs. earlier), man's year of birth (1950+, 1945–1949, 1940–1944 vs. earlier), years of education (13+ vs. others), the man's occupational social class (continuous), wife's social class (highest group, vs. all others), North African origin (vs. all other ethnic groups and rabbis and students in Talmud academies (ever vs. never).
[a]Additionally adjusted for male offspring (1+ vs. none).
[b]Additionally adjusted for stillbirths (1+ vs. none).

exposure of men to ionizing radiation. Experimental irradiation of male rodents has been shown to cause stillbirth in offspring [78]. An excess of stillbirths was detected among male workers in a nuclear reprocessing plant in Cumbria, UK [79]; however, a subsequent study of other nuclear workers was interpreted as negative, although there were some minor increases observed in the risk of stillbirth for men with heavier exposures to radiation [80]. Ecologic data also links background radiation to stillbirths [81].

The risk of stillbirth is increased with paternal ageing, independently of maternal age [82,83]. The incidence of prostate cancer in sons has also be related to paternal age [84] as has the incidence of numerous other adverse outcomes ranging from early fetal death [85] and birth defects [86] to childhood cancers [87,88], and neuropsychiatric disorders [89–91]. A unifying hypothesis linking these diverse outcomes is de novo mutation, known to depend on paternal aging [92–94]. Men's spermatogonial stem cells are constantly dividing and may give rise to clones carrying acquired mutations, as do any somatic cells. One plausible explanation, then, for the link between stillbirth in the offspring and excess risk of prostate cancer in fathers might be de novo mutation, due to the combination of exposure to mutagens and genetic susceptibilities [95]. Even in the absence of de novo mutation, however, heritable mutations or variants present in the man could be the direct cause of stillbirth in his offspring, or contribute to fetal susceptibility to environmental causes of stillbirth. There are numerous single gene defects associated with stillbirths; furthermore, it is well known that Mendelian mutations and chromosome anomalies can cause stillbirth [96].

The strength of our prospective study lies in its being based on a well defined cohort with a long duration of follow-up. Information on stillbirths was ascertained in a uniform manner, from wives, many years before the diagnosis of prostate cancer. Similarly, the diagnosis and ascertainment of prostate cancer were reported in a uniform manner through a national registry and should be free of ascertainment bias with respect to stillbirths. Access to health care in Israel is universal, and there is no reason to think that men whose wives had a stillbirth many years earlier would differ from others in ascertainment or registration of prostate cancers. An additional advantage is that all of the men in this study were married. The extreme religious conservatism of this population adds to the likelihood that husbands were indeed the biological fathers of their reported offspring. In many other developed countries, in comparison, a high proportion of pregnancies result from extra-marital liaisons.

The second sub-cohort, with wives interviewed in 1974–1976, has an additional advantage of being broadly representative of the population of fertile men. Moreover, although the first cohort, interviewed in 1965–1968, is limited by its restriction to the clients of public clinics, we have been able to describe the differences between those who were interviewed and those who were not and adjust for a number of confounders. There is no reason to suspect that unmeasured characteristics of the men from the first sub-cohort would bias the data significantly with respect to the probability of prostate cancer many years later; furthermore, the similarity of the results from the two sub-cohorts makes this very unlikely.

A limitation is that we do not possess a complete record of all of the offspring born to these men. The cohort of 92,408 births was restricted to a 13 years ''snapshot'' of fertility, and interviews with the women

will have missed any offspring born to the same parents later. Furthermore, although we observed stillbirths directly in the Jerusalem Perinatal Study, with an incidence of 10.0/1,000 total births, we could not base our analyses on these observed stillbirths, because we were unable to trace their fathers. The Jerusalem Perinatal Study did not record the identity numbers of fathers and while stillbirths are reported to the health authorities in Israel, they are not entered into Israel's Population Registry. For this reason, we based the study on the wives' reports of their earlier pregnancies. In order to permit tracing, all of the wives must have given birth, at some time, to a live offspring. Thus, the study excludes men who were completely infertile, and may include some misclassification in that some men might have sired stillborn offspring after 1976. Since such stillbirths would be rare, i.e. ~1%, this misclassification would be unlikely to bias the relative risk more than very minimally.

Another limitation is that we do not have information on measures of severity of disease, such as Gleason score, and have no knowledge of individual screening behavior. The use of PSA, introduced in 1991, has caused an increase in the diagnosis of prostate cancer in our cohort, especially, as in the US, among better educated and more affluent men [97,98]. Because of this, and because stillbirths are strongly related to lower social class, our adjustments for social class, education and calendar time led to an increase in the RR associated with stillbirth, beyond the age-adjusted RR. In the men whose wives had stillbirths, we observed no cases of prostate cancer before 1991; but none were expected. Overall, we detected no violation of the proportional hazards assumption. Furthermore, there was no obvious effect of stillbirths on age at diagnosis or cohort year of birth, so we consider it unlikely that the introduction of the PSA test led to a spurious association of risk of prostate cancer with stillbirth.

Because of the aforementioned limitations, our study should be regarded as ''hypothesis-generating''. Before stillbirths can be regarded to be a risk factor or risk marker for prostate cancer, our observation should be confirmed in other populations. Our findings are consistent, however, with the hypothesis that the raised risk of prostate cancer in men with no live male offspring, previously observed in this cohort [1] might be explained by a selective loss of male fetuses in later pregnancy. This, too, should be verified in other populations.

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