Risk of prostate cancer for men fathering through assisted reproduction: nationwide population based register study

Yahia Al-Jebari,[1] Angel Elenkov,[1,2,3] Elin Wirestrand,[1] Indra Schütz,[1] Aleksander Giwercman,[1,3] Yvonne Lundberg Giwercman[1]

[1]Department of Translational Medicine, Lund University, Malmö, Sweden

[2]Department of Urology, Medical University Sofia, Sofia, Bulgaria

[3]Reproductive Medicine Center, Skåne University Hospital Malmö, Malmö, Sweden

Correspondence to: Y Al-Jebari
yahia.al-jebari@med.lu.se
(or @YahiaAlJebari on Twitter;
ORCID 0000-0002-2474-0471)

ABSTRACT

OBJECTIVE
To compare the risk and severity of prostate cancer between men achieving fatherhood by assisted reproduction and men conceiving naturally.

DESIGN
National register based cohort study.

SETTING
Sweden from January 1994 to December 2014.

PARTICIPANTS
1 181 490 children born alive in Sweden during 1994-2014 to the same number of fathers. Fathers were grouped according to fertility status by mode of conception: 20 618 by in vitro fertilisation (IVF), 14 882 by intra-cytoplasmic sperm injection (ICSI), and 1 145 990 by natural conception.

MAIN OUTCOME MEASURES
Prostate cancer diagnosis, age of onset, and androgen deprivation therapy (serving as proxy for advanced or metastatic malignancy).

RESULTS
Among men achieving fatherhood by IVF, by ICSI, and by non-assisted means, 77 (0.37%), 63 (0.42%), and 3244 (0.28%), respectively, were diagnosed as having prostate cancer. Mean age at onset was 55.9, 55.1, and 57.1 years, respectively. Men who became fathers through assisted reproduction had a statistically significantly increased risk of prostate cancer compared with men who conceived naturally (hazard ratio 1.64, 95% confidence interval 1.25 to 2.15, for ICSI; 1.33, 1.06 to 1.66, for IVF). They also had an increased risk of early onset disease (that is, diagnosis before age 55 years) (hazard ratio 1.86, 1.25 to 2.77, for ICSI; 1.51, 1.09 to 2.08, for IVF). Fathers who conceived through ICSI and developed prostate cancer received androgen deprivation therapy to at least the same extent as the reference group (odds ratio 1.91; P=0.07).

CONCLUSIONS
Men who achieved fatherhood through assisted reproduction techniques, particularly through ICSI, are at increased risk for early onset prostate cancer and thus constitute a risk group in which testing and careful long term follow-up for prostate cancer may be beneficial.

WHAT IS ALREADY KNOWN ON THIS TOPIC

As prostate cancer and many forms of infertility are androgen related, a possible link between them has been studied, yielding contradictory results

Studies in older men using childlessness as a proxy for infertility show that childless men have a lower risk of prostate cancer

Studies in younger men, assessing fertility by means of semen parameters, indicate a higher risk of prostate cancer

Previous studies have been limited by small numbers of study participants, self reported diagnoses, or short follow-up time

WHAT THIS STUDY ADDS

This large register based study show that men fathering children through assisted reproduction have a 30-60% increased risk of prostate cancer compared with men conceiving naturally

They have almost twice the risk of developing early onset prostate cancer, before 55 years of age

Men fathering children through assisted reproduction seem to be at higher risk for prostate cancer, so the benefits of prostate cancer screening should be considered for this group

Introduction

Prostate cancer and male infertility are both very common disorders, affecting approximately 10% and 8%, respectively, of all men in Western societies.[1 2] As prostate cancer and many forms of infertility are androgen related, the possible link between these disorders has been investigated previously. Three American studies have reported an increased risk of prostate cancer in men with impaired semen quality,[3-5] whereas three Scandinavian studies and one American study indicated a lower risk of prostate cancer in childless men.[6-9] This finding was recently confirmed in a meta-analysis summarising 10 individual studies.[10] Others found no relation between fatherhood and the risk of prostate cancer.[11-14]

Neither fatherhood status nor sperm parameters represent ideal markers of male infertility. Whereas childlessness may be related to the female partner's subfertility, the opportunity to start a family, or personal choice, and thus attributable to social rather than biological factors, semen parameters such as sperm concentration, morphology, and motility are subject to both laboratory and intra-individual variation. Nevertheless, for many infertile men, fatherhood is still possible through use of powerful assisted reproductive techniques. For men with very few sperm (oligozoospermia), or spermatozoa with poor progressive motility (asthenozoospermia), the only option for fatherhood is intracytoplasmic sperm injection (ICSI), in which a sperm is injected into an egg and the embryo put back into the uterus. This is also the only possibility for men with azoospermia, from whom gametes can be microsurgically gathered from the epididymis or testis. For men who do not have such severely deficient spermatogenesis, conventional in vitro fertilisation (IVF), in which sperm are allowed to fertilise retrieved oocytes in a laboratory dish, is the standard procedure. In Sweden, ICSI treatment

is mainly used in cases with significantly impaired semen quality, with male factor infertility being the major indication for ICSI.[15][16]

The objective of this study was to use compulsory national registries containing information on prostate cancer diagnoses and infertility treatments to investigate whether the risk of prostate cancer in men who became fathers through IVF or ICSI, reflecting the grade of hampered spermatogenesis, differed in terms of incidence, age at onset, and, where applicable, severity from men who achieved fatherhood naturally. Such information could be important for defining clinical routines for follow-up of men undergoing fertility treatment.

Methods

Registers and study populations

We retrieved data on all children born alive in Sweden during the period 1994-2014 (n=2 108 569), as well as their fathers, from the Swedish Medical Birth Register and the Swedish Multi-generation Register. We excluded children with missing paternal identification numbers. We matched the remaining records with the Swedish National Quality Register for Assisted Reproduction. The Swedish Cancer Registry, the Swedish Register of Education, and the Swedish Cause of Death Register supplied the paternal prostate cancer diagnoses, paternal education data, and date of death, respectively. Reporting of cancer diagnoses to the national Swedish Cancer Registry is mandated by law for all newly diagnosed cancers, with an approximated completeness of 96%,[17] ensuring a complete assessment of prostate cancer diagnoses. Similarly, reporting of fertility treatments is mandatory, in both private and public clinics, with coverage close to 100%. Data on patients undergoing intrauterine insemination, which is an uncommon procedure in Sweden, was not collected. Thus, in this paper, assisted reproductive techniques refers to ICSI and IVF. As ICSI was first used in 1992, virtually all fathers who conceived through ICSI in Sweden are likely to be included in our cohort.

To avoid bias introduced by fathers being counted multiple times, we paired the birth record of the first child born within the cohort interval with the father. This resulted in 1 181 490 children born to the same number of fathers (fig 1). Prostate cancer was defined according to ICD-7 (international classification of diseases, 7th revision) diagnosis code (177) and early onset prostate cancer according to European Association of Urology guidelines[18] (that is, diagnosed before the age of 55).

Using data from the Swedish Prescribed Drug Register, available from July 2005 to November 2016, we identified men who had received androgen deprivation therapy. This is indicated only in cases of locally advanced or metastatic prostate cancer and not in low risk malignancies.[19] Thus, androgen deprivation therapy can act as a proxy for the severity and clinical significance of malignancy. We identified men receiving androgen deprivation therapy, with the date of their first prescription, by parsing for the following drugs: abiraterone acetate, buserelin, cyproterone acetate, degarelix, enzalutamide, flutamide, goserelin, histrelin acetate, leuprorelin, megestrol acetate, nilutamide, and triptorelin.

As receiving testosterone replacement therapy has an unknown effect on risk of prostate cancer, we excluded these men identified by data from the Swedish Prescribed Drug Register in a sensitivity analysis. Prescription of testosterone at any time led to exclusion (336 ICSI treated fathers, 212 IVF treated fathers, and 7495 reference fathers).

Statistical analysis

We grouped the fathers according to mode of conception of their child; ICSI, IVF, or natural conception (reference group). We constructed Kaplan-Meier survival curves stratified on the aforementioned groups, with accompanying log rank tests. We used Cox regression to estimate hazard ratios. In the Cox regressions analyses, we corrected for paternal age by adjusting for fathers' age at childbirth (continuous). We followed the fathers from conception of the child until diagnosis of prostate cancer, death, or end of follow-up (31 December 2014). We estimated the date of conception by using gestational length data from the Medical Birth Register. To adjust for socioeconomic status, the Cox model was adjusted for the father's education level (years of formal education, categorical: ≤10, 11-14, ≥15, or missing data).

We tested the assumption of proportionality of hazards by the significance level of the interaction between prostate cancer and the natural logarithm of time within the full Cox regression model with all covariates. We further investigated any evidence of non-proportionality (P<0.05) by estimating hazard ratios for restricted time intervals.

To investigate whether men achieving fatherhood by assisted means had an altered risk of early onset prostate cancer, we did an analysis in which we defined an event as prostate cancer diagnosed before age 55. Follow-up was as above, with the fathers being right censored when they reached age 55. This analysis was adjusted for the same covariates as before (paternal age and paternal education level). We also combined the fathers treated with ICSI and those treated with IVF into one group so that a combined risk estimate could be obtained for men becoming fathers through assisted reproduction techniques.

As the follow-up for each father started from conception of the child, men with a prostate cancer diagnosis before that point were excluded, leading to nine ICSI treated fathers, one IVF treated father, and 28 naturally conceiving fathers being excluded from the analyses. However, as cancer treatment may cause subsequent fertility problems, we did a separate sensitivity analysis in which fathers who had been diagnosed as having any cancer (ICD-7: 140-207.9) before child conception, not only prostate cancer, were also excluded (ICSI, n=451; IVF, n=171; natural conception, n=5179).

As ICSI is indicated in more severe forms of male infertility (azoospermia, severe oligozoospermia) and IVF is used in female infertility, combined with mild or no male infertility,[15 16] we tested for a trend between level of infertility and prostate cancer. This assumed an equidistant stepwise function for the level of infertility among fathers conceiving naturally, via IVF, or via ICSI (continuous variable coded: natural conception=0, IVF=1, ICSI=2).

Among all fathers with prostate cancer, we compared the fathers who conceived through ICSI and IVF with those who conceived naturally, to estimate the risk for receiving androgen deprivation therapy after diagnosis of prostate cancer. As prescriptions for androgen deprivation therapy could not be ascertained before July 2005, only prostate cancer diagnoses after this date were included in this analysis. After these exclusions 52 ICSI treated, 68 IVF treated, and 2967 reference fathers remained. This analysis also serves to detect overdiagnosis of clinically insignificant cases of prostate cancer among men undergoing assisted reproduction, owing to their contacts with the healthcare system. This potential bias would likely lead to these men being diagnosed as having prostate cancer at an earlier age, with lower grade, and therefore generally not being treated with androgen deprivation therapy. Conversely, observing an equal or higher risk of androgen deprivation therapy for men undergoing assisted reproduction would indicate no such bias. For this analysis, we constructed a binary logistic regression model, adjusted for the father's age

at prostate cancer diagnosis (continuous) and paternal educational level, yielding odds ratios, with an odds ratio below 1 indicating possible bias resulting in more diagnoses of low grade prostate cancer among the assisted reproduction groups—for example, due to better access to prostate specific antigen screening. Conversely, an odds ratio of 1 or above points to an increase in prevalence of clinically relevant prostate cancer, which would likely be diagnosed regardless of whether those men were in contact with the healthcare system.

We also did sensitivity analyses in which men receiving testosterone were excluded. We calculated risk estimates for prostate cancer and for early onset prostate cancer by using the same Cox regression method as above.

We used SPSS version 25 and R version 3.5.0 with the ggplot2 package for statistical analyses. All analyses were two sided, and we defined $P<0.05$ as statistically significant.

Patient and public involvement
No patients were involved in the design of this study, nor were any patients involved in the implementation of it or consulted on the reporting of the results. There are no plans to disseminate the results to the research cohort or to relevant patient communities.

Results
Of 1 181 490 fathers, 20 618 (1.7%) had undergone IVF during the study period, 14 882 (1.3%) had undergone
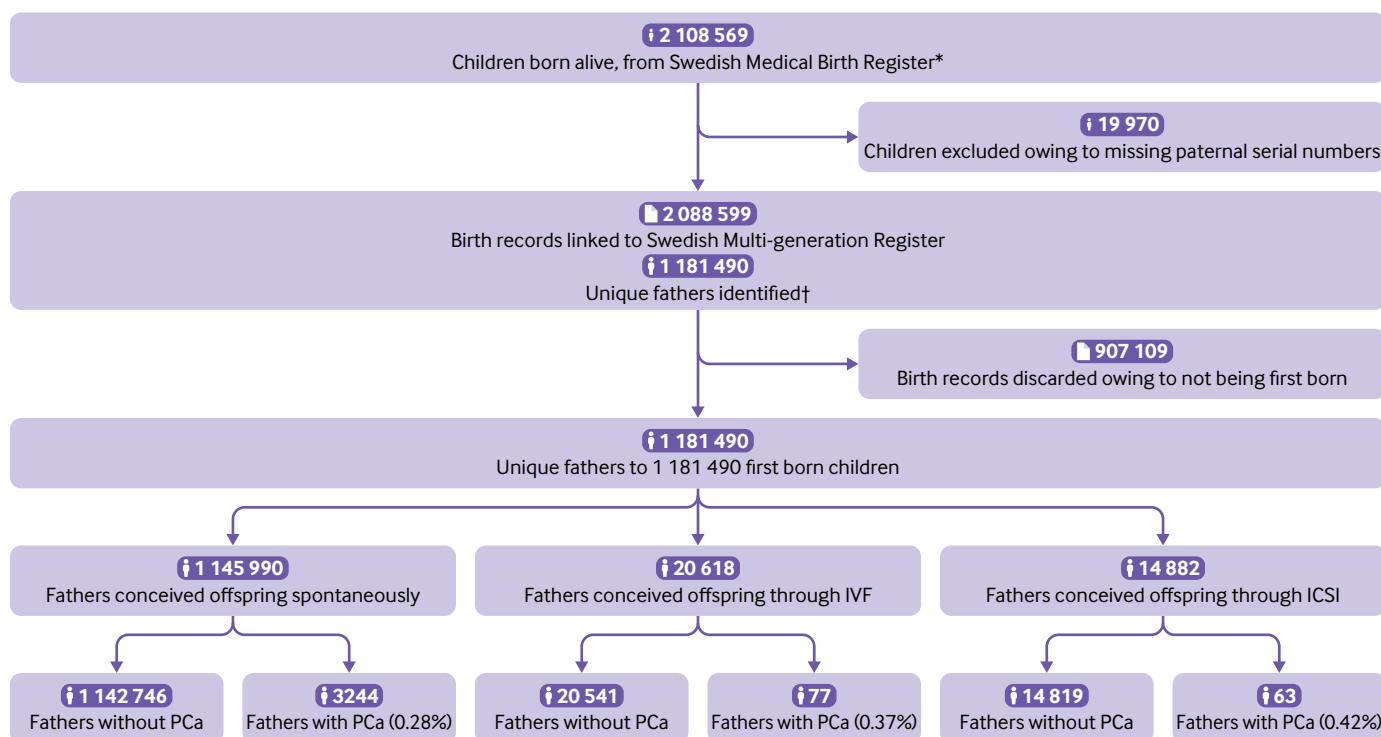

Fig 1 | Flowchart of inclusion process and register linkage. *1 January 1994 to 31 December 31. †Registers linked to Swedish Education Register, Swedish National Quality Register for Assisted Reproduction, and Swedish Cancer Registry. PCa=prostate cancer; ICSI=intracytoplasmic sperm injection; IVF=in vitro fertilisation

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Table 1 | Characteristics of fathers who conceived offspring naturally, through intracytoplasmic sperm injection (ICSI), and through in vitro fertilisation (IVF). Values are numbers (percentages) unless stated otherwise

Characteristics	Fathers conceiving naturally (n=1 145 990; 97.0%)	Fathers conceiving by IVF (n=20 618; 1.7%)	Fathers conceiving by ICSI (n=14 882; 1.3%)
Mean (SD) age at birth of child, years	32.5 (6.2)	36.6 (5.3)	36.9 (6.0)
Mean (SD) age at end of follow-up*, years	44.0 (9.0)	45.9 (8.1)	45.2 (7.9)
Years of formal education:			
<10	139 012 (12.1)	1549 (7.5)	1205 (8.1)
10-14	648 789 (56.6)	10 631 (51.6)	7862 (52.8)
≥15	348 081 (30.4)	8375 (40.6)	5754 (38.7)
Missing	10 108 (0.9)	63 (0.3)	61 (0.4)
All prostate cancer:			
Fathers with prostate cancer	3244 (0.3)	77 (0.4)	63 (0.4)
Mean (SD) age at diagnosis, years	57.1 (6.9)	55.9 (5.9)	55.1 (7.0)
Early onset prostate cancer (diagnosis age <55)	1274 (39.3)	39 (51)	29 (46)
Prostate cancer, excluding cases occurring before child conception:			
Fathers with prostate cancer	3216 (0.3)	76 (0.4)	54 (0.4)
Mean (SD) age at diagnosis, years	57.2 (6.9)	56.1 (5.8)	55.4 (6.7)
Mean (SD) time between child conception and diagnosis, years	14.5 (4.7)	13.3 (5.2)	9.5 (4.6)
Early onset prostate cancer (diagnosis age <55)	1257 (39.1)	38 (50)	25 (46)
Androgen deprivation therapy†:			
Fathers treated with androgen deprivation therapy	387§/2967 (13.0)	8/68 (12)	10/52 (19)
Mean (SD) age at start of therapy, years	60.2 (7.6)	57.0 (4.6)	56.4 (8.8)
Early onset prostate cancer (diagnosis age <55 years)	105 (8.4)	3 (8)	5 (20)

*End of follow-up in Cancer Registry (31 December 2014). Deaths not accounted for.
†Patients receiving androgen deprivation therapy within 1 year of prostate cancer diagnosis. Excluding cases occurring before child conception or diagnosed before 1 July 2005.
§Including 12 cases in which androgen deprivation therapy was prescribed in the week preceding prostate cancer diagnosis date.

ICSI, and 1 145 990 (97.0%) had conceived children by natural conception. Table 1 shows characteristics of the fathers. The total follow-up time was 14 389 198 person years. The mean age at childbirth of both IVF and ICSI treated fathers was 37 years, whereas the fathers who conceived naturally were 4 years younger on average. Of the men who sired pregnancies naturally, 3244 (0.28%) were diagnosed as having prostate cancer, compared with 77 (0.37%) in the IVF group and 63 (0.42%) in the ICSI group. After exclusion of cases of prostate cancer before conception, 3216 (0.28%), 76 (0.37%), and 54 (0.36%) had been diagnosed as having prostate cancer in the reference, IVF, and ICSI groups. The ICSI treated fathers had the youngest mean age of onset (55.4 years), on average almost 2 years younger than the reference group.

In the entire cohort, men who had undergone ICSI treatment had a statistically significantly increased risk of prostate cancer (hazard ratio 1.64, 95% confidence interval 1.25 to 2.15; P<0.001) compared with natural conception (table 2; fig 2). IVF fathers also had a statistically significantly increased risk, but of a lesser magnitude (hazard ratio 1.33, 1.06 to 1.66; P=0.02) compared with natural conception. We detected evidence of non-proportionality for ICSI, but not IVF, compared with natural conception (interaction with log (time), P=0.01). The adjusted hazard ratios for the first and second halves of follow-up were 2.22 (1.56 to 3.16; P<0.001) and 1.18 (0.78 to 1.80; P=0.44), respectively. In all other Cox models, the P value for the interaction was greater than or equal to 0.05.

Moreover, both ICSI treated fathers and IVF treated fathers had a statistically significantly increased risk of early onset prostate cancer (hazard ratio 1.86, 1.25 to 2.77 (P=0.002) for ICSI; 1.51, 1.09 to 2.08 (P=0.01) for IVF) (fig 3). Table 2 shows unadjusted risk estimates.

Men who became fathers through assisted reproduction techniques (combined ICSI and IVF) had a statistically significantly increased risk of prostate cancer (odds ratio 1.44, 1.21 to 1.71; P<0.001) and

Table 2 | Unadjusted and adjusted risk estimates for prostate cancer.

Outcome	Fathers conceiving by IVF compared with natural conception		Fathers conceiving by ICSI compared with natural conception	
	Risk estimate (95% CI)	P value	Risk estimate (95% CI)	P value
Prostate cancer:				
Unadjusted hazard ratio	2.09 (1.66 to 2.62)	<0.001	3.12 (2.38 to 4.08)	<0.001
Adjusted hazard ratio	1.33 (1.06 to 1.66)	0.02	1.64 (1.25 to 2.15)	<0.001
Early onset prostate cancer:				
Unadjusted hazard ratio	2.93 (2.12 to 4.05)	<0.001	3.66 (2.46 to 5.44)	<0.001
Adjusted hazard ratio	1.51 (1.09 to 2.08)	0.01	1.86 (1.25 to 2.77)	0.002
Androgen deprivation therapy:				
Unadjusted odds ratio	0.89 (0.42 to 1.87)	0.76	1.59 (0.79 to 3.19)	0.19
Adjusted odds ratio	0.99 (0.47 to 2.10)	0.98	1.91 (0.94 to 3.88)	0.07

ICSI=intracytoplasmic sperm injection; IVF=in vitro fertilisation.
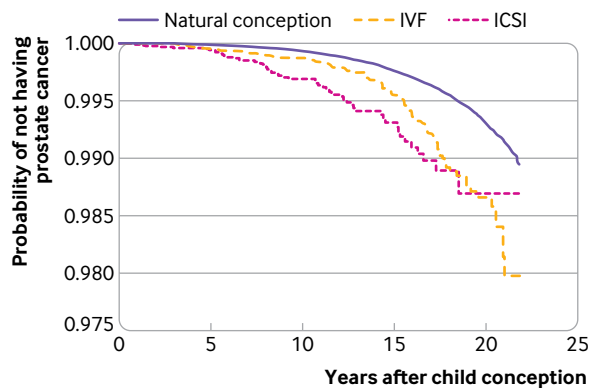
Natural conception

1 145 962	940 084	692 333	454 698	181 249

IVF

20 617	15 274	9504	5007	1535

ICSI

14 873	10 509	6099	2593	184

Fig 2 | Kaplan-Meier function for prostate cancer in fathers who conceived through intracytoplasmic sperm injection (ICSI) and in vitro fertilisation (IVF), compared with natural conception. Numbers are fathers remaining at risk at 5 year intervals after child conception. Log rank P<0.001

early onset prostate cancer (1.63, 1.26 to 1.63, P<0.001) compared with men achieving fatherhood naturally. When we excluded fathers who were diagnosed as having any cancer before their offspring's conception date, ICSI treated fathers still had a statistically significant increased risk of prostate cancer (hazard ratio 1.70, 1.29 to 2.22; P<0.001) and of early onset prostate cancer (1.92, 1.29 to 2.86; P=0.001). Similarly, IVF treated fathers retained their increased risk for prostate cancer (hazard ratio 1.30, 1.03 to 1.64; P=0.02) and early onset prostate cancer (1.45, 1.04 to 2.02; P=0.03). We detected a statistically significant trend for the association of level of infertility and prostate cancer
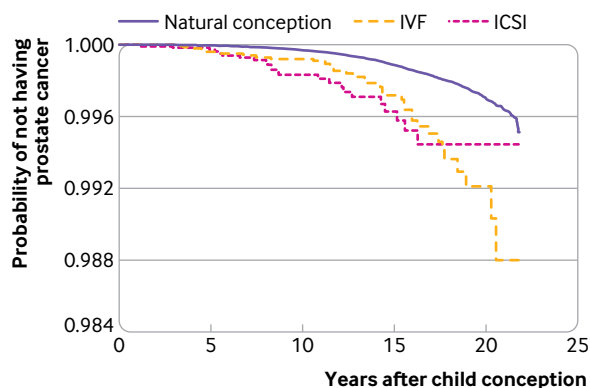
Natural conception

1 141 989	930 381	670 523	412 589	137 098

IVF

20 546	15 061	9007	4057	675

ICSI

14 734	10 217	5674	2064	92

Fig 3 | Kaplan-Meier survival function for early onset prostate cancer in fathers who conceived through intracytoplasmic sperm injection (ICSI) and in vitro fertilisation (IVF), compared with natural conception. Numbers are fathers remaining at risk at 5 year intervals after child conception. Log rank P<0.001

(odds ratio$_{natural, IVF, ICSI}$ 1.29, 1.15 to 1.45; P<0.001). Similarly, we detected a trend for the association between level of infertility and the risk of early onset prostate cancer (odds ratio$_{natural, IVF, ICSI}$ 1.40, 1.18 to 1.66; P<0.001).

The ICSI treated fathers with prostate cancer also had the highest rate of receipt of androgen deprivation therapy (19.2%) compared with the reference group (13.0%) and IVF group (11.8%). We saw no indication that men who underwent assisted reproduction were more often diagnosed as having low grade prostate cancer than men who conceived naturally (odds ratio 1.91, 0.94 to 3.88 (P=0.07) for ICSI; 0.99, 0.47 to 2.10 (P=0.98) for IVF). Exclusion of men who received testosterone replacement therapy had a negligible effect on hazard ratios for prostate cancer and for early onset prostate cancer for both the ICSI and IVF groups.

Discussion

The main conclusion of this study, comprising virtually all men fathering a child in Sweden during two decades, is that men who achieved fatherhood through assisted reproduction had a remarkably high risk of prostate cancer. Fathers who used ICSI had a 60% higher risk and those who used IVF had a 30% higher risk, compared with men who conceived naturally. The increase in risk was most pronounced before the age of 55 years and was still present after exclusion of men who had been treated for any cancer and therefore with potentially gonadotoxic treatments before the child's conception.

Strengths and weaknesses of study

The strengths of this study are access to population based datasets and the completeness of the registries. A drawback is the lack of data in the registries on fertility treatment in men who did not succeed in becoming fathers. Hence, the most severe cases may not have been included. However, our results, specifically the trend showing an increasing risk of prostate cancer and of early onset prostate cancer, may indicate that it is the underlying level of infertility that is associated with the man's risk of this malignancy. This might indicate that our results could be generalised to men undergoing assisted reproduction techniques without achieving fatherhood or possibly even to infertile men in general. This would align well with previous studies showing increased risk of prostate cancer for men with poor semen parameters.[3-5]

Furthermore, data on prostate specific antigen were not available. Such data could have provided direct evidence as to whether men undergoing ICSI receive closer follow-up than their counterparts, but the registries do not include this information. Finally, data on men who died from prostate cancer before they had a chance to become fathers are lacking. However, with a mean age of only 37 years for the ICSI/IVF treated fathers and 32 years for those who conceived naturally, the effect of such selection bias can be considered small. Men attaining fatherhood through IVF and ICSI were on average older and also more well educated at

the birth of their offspring. However, the presented risk estimates were adjusted for these factors.

The evidence of non-proportionality for ICSI treated men indicates a higher risk in the first decade after conception but no elevated risk thereafter. This might be due to an insufficient number of ICSI treated men with long follow-up, because few men were treated with ICSI in the 1990s, yielding uncertain risk estimates. However, as ICSI treated men have an increased risk of early onset prostate cancer, but not of the late onset variety, this is could be reflecting aetiological differences between early and late onset of prostate malignancy.[20]

Strengths and weaknesses in relation to other studies

The reports indicating a lower risk of prostate cancer in childless or infertile men generally included men with a mean age of 60 years or above,[6-10 21] meaning that those with early onset and more aggressive prostate cancer may already have died from their disease. Consequently, studies based on follow-up of younger men with fertility problems,[3-5] including this report, will tend to include cases of early onset prostate cancer. Studies on older men and their risk of prostate cancer may fail to find this risk increase or even come to the opposite conclusion. However, whereas previous studies relied on smaller datasets, sometimes with self reported childlessness and short follow-up, our study is based on more than one million men and up to 20 years of follow-up.

Men undergoing assisted reproduction owing to an increased risk of hypogonadism may have been candidates for testosterone replacement therapy and may therefore have been tested for prostate specific antigen more frequently to exclude ongoing prostate cancer.[22] This bias could lead to a detectable increased risk among IVF and ICSI treated fathers. However, excluding men receiving testosterone had a negligible effect on the risk of prostate cancer, indicating no such bias. Furthermore, few men undergoing assisted reproduction are likely to have prostate specific antigen tests, as these are usually administered only to older men. That said, if such testing, being a consequence of these men being in contact with the health service, is the reason why ICSI treated men are diagnosed as having prostate cancer at younger ages, one would expect a decreased administration of androgen deprivation therapy among ICSI treated men, which is the opposite of what is observed. The same would apply to ascertainment bias, to which the outcome of prostate cancer is particularly prone to. However, increased medical attention for men seeking treatment for infertility can explain neither the almost doubled rate of androgen deprivation therapy among ICSI treated fathers nor the trend seen with the level of infertility.

Meaning of study: possible explanations and implications for clinicians and policy makers

This work shows that men fathering children by assisted reproduction are a high risk group for prostate cancer at early ages. As clinicians have for many years noted that early onset prostate cancer is associated with poor prognosis, even before the era of prostate specific antigen screening, men undergoing assisted reproduction may merit further attention and comprise an easily accessible category of patients who may benefit from early screening. Screening by prostate specific antigen testing seems to be the most appropriate, most cost effective, and least invasive first line method for early detection of prostate cancer, and applying it for men treated with assisted reproduction could be beneficial. We would, therefore, welcome studies in other cohorts investigating the risk of prostate cancer in men being treated for infertility and studies on the efficacy and benefits of screening for this risk group, similarly to what is currently offered for other high risk groups.

Unanswered questions and future research

This study was limited mainly to men with prostate cancer diagnoses early in life. As ICSI has been used only since the 1990s, detecting late onset prostate cancer in these men requires longer follow-up and is a matter for future research.

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