Long-term Residential Exposure to Air Pollution and Risk of Testicular Cancer in Denmark: A Population-Based Case–Control Study

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ABSTRACT

Background: The incidence rate risk of testicular cancer has increased over the last four decades, and the most significant increase has been among Caucasian men in Nordic countries. Second-generation immigrant studies indicate a significant role of environmental exposure in testicular cancer.

Methods: We conducted a nationwide register-based case–control study including 6,390 testicular cancer cases registered in the Danish Cancer Registry between 1989 and 2014. Up to four age-matched controls for each case ($n = 18{,}997$) were randomly selected from the Civil Registration System. Ambient air pollution levels were estimated at addresses of cases and controls with a state-of-the-art air pollution modeling system.

Results: We mostly found ORs close to 1.00 and with 95% confidence intervals (CI) spanning 1.00. Exposure during the year preceding birth was associated with ORs for nitrogen dioxide (NO_2) of 0.87 (95% CI, 0.77–0.97) per 10 $\mu g/m^3$ and for organic carbon of 0.84 (95% CI, 0.72–0.98) per 1 $\mu g/m^3$. Exposure during the first 10 years of life was associated with ORs for organic carbon of 0.79 (95% CI, 0.67–0.93) per 1 $\mu g/m^3$, for ozone (O_3) of 1.20 (95% CI, 1.07–1.34) per 10 $\mu g/m^3$, and for secondary inorganic aerosols of 1.07 (95% CI, 1.00–1.15) per 1 $\mu g/m^3$.

Conclusions: Early-life exposure to NO_2 and organic carbon (OC) was associated with lower risk for testicular cancer whereas early-life exposure to O_3 and secondary inorganic aerosols (SIA) was associated with higher risk.

Impact: We report both positive and negative associations between ambient air pollutants and risk of testicular cancer, dependent on pollutant, exposure time window, and age at diagnosis. This is the first study to investigate such associations.

Introduction

Testicular cancer is rare and accounts for 1% of all cancers in men, but it has public health significance because it is the most common cancer among men aged 15 to 40 (1). The risk of testicular cancer has increased over the last four decades and the most significant increase has been among Caucasian men in Nordic countries (2). The incidence rates in Nordic countries (primarily Caucasians) is 11.5 per 100,000 men, whereas those among Black and Asian men are 1 to 2 per 100,000 (3, 4). There are two main types of testicular cancer, germ cell and non–germ cell tumors (5). Germ cell tumors are derived from multi-potential germ cells, mainly teratomas, and seminoma, and account for 97% of all testicular cancers, whereas non–germ cell tumors are derived from testis' support cells and represent 3% of all testicular cancers. The testicular cancer patient often presents with either painless enlargement of testis or symptoms related to metastases such as hemoptysis from lung deposits or endocrine effects such as gynecomastia. Due to recent advances in diagnosis and treatment options, the prognosis of testicular cancer is very good, even after metastases (6).

The main known risk factor for developing testicular cancers is cryptorchidism, also known as undescended testis; testicular cancer risk increases five to 10 times among men born with cryptorchidism as compared to others (7, 8). Other risk factors include Klinefelter syndrome, which is the most common sex chromosome abnormality in which the affected male carries an additional X chromosome (9). This additional X chromosome results in hypogonadism and an increased risk of testicular cancer (10). Family history of testicular cancer among first-degree relatives (father and brothers; refs. 11–13), Caucasian men (14), human immunodeficiency virus (HIV) infection (15), body height (16), and a history of inguinal hernia (17) are other established risk factors of testicular cancer.

Increasing incidence rates of testicular cancer over the last four decades suggests that environmental exposure and lifestyle have an essential role in the testis cancer etiology. The increasing incidence of testicular cancer among young adults also suggests that early-life exposure may be important for disease development. Swedish and Danish second-generation immigrant studies reported testicular cancer risk to be similar to the country of residence and not that of their parents (18, 19), which also points at environmental and or lifestyle as important for testis cancer etiology. Nevertheless, no prior study has investigated a possible link between ambient air pollution exposure and the risk of testicular cancer.

Several animal and human studies have investigated the effect of air pollution exposure as a hormone disruptor (20) and on male infertility (21), and both hormone disruptors and male infertility can increase the risk of testicular cancer (22). Human studies analyzing presence of endocrine-disrupting chemicals in blood samples of young

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males reported a significant association with testicular cancer (23–25). Fetal exposure to pollutants, especially those that can act as hormone disruptors and mimic the estrogen effect, can increase the risk of germ cell tumors (26). Diesel exhaust particles encompass various substances with estrogenic and antiandrogen properties, and exposure, especially during fetal life, can increase the risk of testicular cancer in mice (27). Occupational and residential exposure to pollutants with hormone disrupter characteristics have shown mixed results. Occupational exposure to 1,1-dichloro-2,2-bis-ethylene (28) and residential exposure to polychlorinated biphenyls (23) was associated with increase the risk of testicular germ cell cancer, but other studies did not show similar results (29, 30).

Exposure to ambient air pollution has been negatively associated with sperm morphology in animal and human studies (31). A respirable fraction of particulate matter can act as a transporter for proven endocrine disruptor polyaromatic hydrocarbons (PAH) (32), which can negatively affect spermatogenesis directly or via the hypothalamic-pituitary axis (33) but a further link with an increased risk of testicular cancer has not been established. Long-term exposure to air pollution, specifically nitrogen dioxide (NO_2), ozone (O_3), and particulate matter (PM), can trigger oxidative stress and chronic inflammatory reactions (34). Long-term high level of oxidative stress can results in low sperm quality and quantity via lipid peroxidation, DNA damage, and oxidation of proteins in spermatozoa (35). Testicular cancer risk is high among men with abnormal semen characteristics (36).

Based on the previous observations of air pollutants with hormone disrupting characteristics and causing oxidative stress and chronic inflammation, we hypothesized that air pollution is associated with the incidence of testicular cancer. The aim of the present study was to investigate if outdoor air pollution at the residence is associated with the risk of testicular cancer.

Materials and Methods

Study population

We conducted a register-based matched case–control study based on the entire Danish population. We identified all patients diagnosed with testicular cancer between 1989 and 2014, aged 20 years or older at the time of diagnosis, and without a previous cancer diagnosis, including a previous testicular cancer, in the Danish Cancer Registry (37); we accepted a previous diagnosis of nonmelanoma skin cancer. We used the International Classification of Diseases 10 (ICD-10) codes C62.0–C62.9 to identify testicular cancer patients. Four age-matched (year/month of birth) controls, free of previous cancer diagnosis (except nonmelanoma skin cancer), and alive at the date of diagnosis of their cases (index date), were randomly selected and matched to each case. Controls were selected from all eligible male individuals in the Danish Civil Registration System (38).

Exposure assessment

Using the unique 10-digit identification numbers, we extracted all the study participants' residential addresses from January 1, 1979, to December 31, 2014, from the Danish Civil Registration System (38). Geographical coordinates at the residential address's front door were attained using municipality code, street, and house number. All addresses were geocoded within 5 m from the front door using the Danish address database. We estimated the annual mean concentration of $PM_{2.5}$, $PM_{2.5}$ constituents, NO_2, O_3, and sulphur dioxide (SO_2) using the high-resolution multiscale air pollution model system DEHM/UBM/AirGIS. The DEHM/UBM/AirGIS model was described in detail previously (39).

In summary, DEHM/UBM/AirGIS combines three models to estimate air pollution levels at a location: (i) The Danish Eulerian Hemispheric Model (DEHM), which calculates regional background concentrations due to long-range transport (40, 41). DEHM estimates both natural and anthropogenic emissions of gases and particles and their precursors. DEHM uses a 3D large-scale chemistry transport model with a spatial resolution of 5.6 km × 5.6 km to estimate regional long-range transport. DEHM also estimates chemical reactions, atmospheric transport, and dispersion of pollutants and the deduction processes in the atmosphere, such as transport dispersion and deposition. DEHM models the primary particles [mineral dust, black carbon (BC), organic carbon (OC), and sea-salt], the secondary inorganic aerosols (SIA) including ammonium (NH_4), sulphate (SO_4), and nitrate (NO_3) in their different chemical forms, and the secondary organic aerosols (SOA) generated from gaseous organic precursors such as volatile organic compounds (VOC), isoprene, etc.; (ii) The Urban Background Model (UBM) uses the SPREAD emission model (42) to estimates contribution from an urban area (39, 43–45) using an average building cover and height for a 1 km × 1 km resolution over Denmark. The UBM estimates the local urban emissions of NO_x and primarily emitted particles originating from all sources (e.g., traffic and residential heating) and also takes into account the regional background concentrations modeled with DEHM (46, 47); and (iii) The Operational Street Pollution Model (OSPM), which models local air pollution levels using traffic intensity, speed, and distribution of vehicle types to calculates contributions from the local traffic in the address street (48). The OSPM also accounts for the detailed information on the street and geometry of buildings surrounding the street (49). OSPM estimates air pollution at a 2-m height at addresses in streets with 500 or more vehicles per day. Comparisons between model predictions and measured concentrations show correlation coefficients between 0.62 and 0.92 for the different pollutants (Supplementary Materials and Methods, text 1). We refer to the Supplementary Materials and Methods for more details about the air pollution model system concerning sources of uncertainty, spatial resolution, and main sources of the pollutants.

We used the average concentrations of air pollutants weighted by the time living at each address during the relevant period. We calculated such time-weighted averages (TWA) of air pollution concentrations over four time periods: the 1 year before birth, the first 10 years of life, 10 to 20 years before the index date (10 years lag), and the last 10 years before the index date. Participants with missing exposure information for 20% or more of the relevant exposure time window were excluded from the final analysis. For periods with missing exposure for less than 20% of the time, the TWA was calculated for the period with known exposure.

Potential confounders

Using the 10-digit unique personal identification number (PIN; ref. 39), information on potential confounders, both at individual and parish levels, was extracted from the registries of Statistics Denmark. The individual-level data included marital status (cohabiting, divorced, and never married), disposable income (calendar year specific quantiles), and attachment to the labor market (blue-collar, lower white-collar, higher white-collar, unemployed, retired). Sociodemographic data were also retrieved at the parish level from Statistics Denmark. We obtained yearly data for the proportion of households living in rented dwellings, the proportion of inhabitants with a manual profession, and the proportion of inhabitants with disposable income in the lower quintile. In 2017, in Denmark, 2160 parishes existed with an average area of 16.2 km^2 (range 0.1–126.2) and a median number of

1,032 inhabitants (range approximately 33–36,000). We used individual and parish level values corresponding to 1 year before the index date to minimize the risk of prediagnostic symptoms influencing sociodemographic variables. We selected the sociodemographic factors based on availability and also because these factors might captures variation in (unknown) environmental/societal factors, which could be responsible for changes in testicular cancer incidence rates. We also extracted health data to identify individuals with HIV infection, born with cryptorchidism, or any congenital malformation of male genital.

Statistical analysis

We used conditional logistic regression analyses to assess the associations between exposure to different pollutants and testicular cancer and estimated ORs with 95% confidence intervals (CI). We adjust for potential confounders in three á priori determined models: Model 1 adjusted for age and calendar time by the matched design; model 2 further adjusted for individual-level characteristics, including cohabiting status, disposable income, and attachment to the labor market. model 3 (our main model) further adjusted for manual labor, income, and homeownership at the neighborhood level. Results for all three models are given in the supplementary materials and methods; due to minor differences in results for the three models we present only results from model 3 in the manuscript text. We performed analysis for TWA exposures of all pollutants over four time periods: the 1 year before birth, the first 10 years of life, 10 to 20 years before the index date (10 years lag), and the last 10 years before index date. We also analyzed if the risk differs for older (≥36 years) and younger (≤35 years) age group testicular cancer patients because the incidence rates for testicular cancer is higher for the age group 20 to 35 years than for those 35+ years indicating that different etiologies might be in play; we tested a possible interaction by introducing an interaction term with a dichotomous variable indicating the age group. We tested deviation from linearity by comparing a decile model with a linear model using the likelihood ratio test; the *P* values ranged between 0.13 and 0.68 indicating no deviation from linearity based on the "last 10-year" exposure time window; thus, we fitted linear models. The uncertainty of the exposure model might have been higher in the early period (supplementary materials and methods). Therefore, we estimated risk for testicular cancer for those diagnosed 1989–1999 and 2000–2014 separately. All statistical analyses were performed in R version 3.2.1.

Data availability

This study was conducted using data from Statistics Denmark. Data are available with the permission of Statistics Denmark (https://www.dst.dk/da).

Results

We identified 6,941 eligible cases and 22,594 eligible age-matched controls for the analysis of exposure during the last 10 years before diagnosis. We excluded cases ($n = 105$) and controls ($n = 103$) with history of cryptorchidism, cases ($n = 10$) and controls ($n = 7$) born with congenital malformation of male genital, cases ($n = 34$) and controls ($n = 52$) with a history of HIV. We further excluded cases ($n = 305$) and controls ($n = 1,618$) with missing exposure information for more than 20% of the 10 years preceding index date, and cases ($n = 74$) and controls ($n = 261$) with a missing value for any covariate. Finally, after the above exclusions, we excluded cases ($n = 23$) and controls ($n = 1,556$) for whom no matched case or control was available resulting in 6,390 cases and 18,997 matched controls for analysis of exposure during the last 10 years before diagnosis (Supplementary Table S1).

Table 1 shows sociodemographic characteristics of cases and controls. Over 60% of the study population was aged 40 or below; income, marital status, and attachment to the labor market were similar between cases and controls. Study participants' area-level sociodemographic characteristics were also similar for cases and controls. The 10-year TWA concentrations of pollutants were similar among cases and controls with a mean exposure among controls of 21.75 $\mu g/m^3$ for NO_2, 13.63 $\mu g/m^3$ for SO_2, 58.99 $\mu g/m^3$ O_3, 18.20 $\mu g/m^3$ for $PM_{2.5}$, 0.85 $\mu g/m^3$ for BC, 1.51 $\mu g/m^3$ for OC, 0.31 $\mu g/m^3$ for SOA, 8.34 $\mu g/m^3$ for SIA, 1.52 $\mu g/m^3$ for NH_4, 3.71 $\mu g/m^3$ for NO_3, 3.11 $\mu g/m^3$ for SO_4, and 4.10 $\mu g/m^3$ for sea-salt (**Table 2**; Supplementary Fig. S1).

Spearman correlation coefficients between air pollutants among controls are reported in Supplementary Table S2 and shows that $PM_{2.5}$ was strongly correlated with secondary inorganic aerosols (Rs = 0.94) and its constituents NH_4 (Rs = 0.87), NO_3 (Rs = 0.90), SO_4 (Rs = 0.94), and SO_2 (Rs = 0.95). O_3 was negatively associated with NO_2 (Rs = −0.98), BC (Rs = −0.91), OC (Rs = −0.84), $PM_{2.5}$ (Rs = −0.54), SOA (Rs = −0.61), SIA (Rs = −0.28), and its constituents.

Table 3 shows associations between risk for testicular cancer and exposure to air pollution during four different time windows. ORs in association with exposure during the last 10 years before diagnosis were close to 1.00 and with CIs spanning 1.00 (**Table 3**); adjustment had minor influence on these ORs (Supplementary Table SS3). The results were similar for those diagnosed between 1989 and 1999 and 2000 and 2014 (Supplementary Table SS4), and for exposure during 10 to 20 years before diagnosis (10-y lag; **Table 3**). **Table 3** also shows that exposure during the year preceding birth was associated with ORs for NO_2 of 0.87 (95% CI, 0.77–0.97) per 10 $\mu g/m^3$ and for OC of 0.84 (95% CI, 0.72–0.98) per 1 $\mu g/m^3$. Exposure during the first 10 years of life was associated with ORs for OC of 0.79 (95% CI, 0.67–0.93) per 1 $\mu g/m^3$, for O_3 of 1.20 (95% CI, 1.07–1.34) per 10 $\mu g/m^3$, and for SIA of 1.07 (95% CI, 1.00–1.15) per 1 $\mu g/m^3$.

The primarily emitted carbonaceous particles showed higher ORs in association with testicular cancer in the older (> = 36 years) than in the younger age group (< = 35 years); ORs for OC were 1.20 among the older and 0.90 among the younger (P for interaction between OC exposure and age group: 0.05). For the other air pollutants, the confidence intervals around the ORs for the younger and older age groups widely overlapped (**Table 4**). Supplementary Fig. S2 shows spline plots of associations between air pollution and risk for testicular cancer.

Discussion

In this large population-based case–control study, we found no overall association between outdoor air pollution at the residence the last decades before the diagnosis and the risk of testicular cancer. Exposure to NO_2 and OC the year before birth and the first 10 years of life was associated with lower risk of testicular cancer whereas exposure to O_3 and SIA during the first 10 years of lift was associated with a higher risk of testicular cancer. Exposure to OC during the last 10 years before the diagnosis was associated with higher risk for testicular cancer diagnosed after 35 years of age.

To the best of our knowledge, this is the first study to investigate a possible association between residential outdoor air pollution and the incidence of testicular cancer. Second-generation immigrant studies from Denmark (19) and Finland (50) reported similar testicular cancer

Table 1. Sociodemographic characteristics of study participants.

Characteristics	Controls[a] (*N* = 18,997) *n* (%)	Cases (*N* = 6,390) *n* (%)
Age at index date		
<40	12,267 (64.6)	4,193 (65.6)
40–50	3,806 (20.0)	1,290 (20.2)
50–60	1,709 (9.0)	551 (8.6)
≥60	1,215 (6.4)	356 (5.6)
Year of testicular cancer diagnosis[b]		
1989–1993	3,838 (20.2)	1,210 (18.9)
1994–1998	2,434 (12.8)	773 (12.1)
1999–2003	3,748 (19.7)	1,215 (19.0)
2004–2008	3,571 (18.8)	1,230 (19.2)
2009–2014	5,406 (28.5)	1,962 (30.7)
Disposal income		
Quintile 1 (low)	4,835 (25.3)	1,519 (23.8)
Quintile 2	4,738 (24.9)	1,605 (25.1)
Quintile 3	4,682 (24.6)	1,668 (26.1)
Quintile 4 (high)	4,742 (25.0)	1,597 (25.0)
Marital status		
Cohabiting	8,033 (42.3)	2,696 (42.2)
Divorced	9,632 (50.7)	3,268 (51.1)
Never married	1,332 (7.0)	426 (6.7)
Attachment to labor market		
Blue collar	8,744 (46.0)	3,067 (48.0)
Lower white collar	4,221 (22.2)	1,340 (21.0)
Higher white collar	2,400 (12.6)	856 (13.4)
Unemployed	1,280 (6.7)	387 (6.1)
Retired	2,352 (12.4)	740 (11.6)
Parish level factors		
Median % of population in manual labor	28	28
Median % of population in 1st income quartile	10	10
Median % of population owning own dwelling	12	13

[a]Controls were matched to cases by gender and birth year and month.
[b]For controls: year of index date.

risk to the country of residence. In contrast, the first-generation immigrants maintained the risk of testicular cancer observed in their country of origin. Thus, environmental factors might play a role in the etiology of testicular cancer. Our study indicates that if air pollution plays a role, early exposure (first 10 years of life) to primary air pollution from local sources (indicated by NO_2, BC, and OC) might be associated with a lower risk for testicular cancer whereas early exposure to secondary pollutants (indicated by O_3 and SIA) might be associated with a higher risk. Late exposure (last 10 years before diagnosis) to OC might be associated with higher risk for testicular cancer among those diagnosed after age 35 but not among those diagnosed at younger ages. These results were based on multiple analyses of combinations of pollutant, exposure time window, and age group and we cannot exclude that they are a result of chance. It seems counterintuitive that exposure to some air pollutants reduces the risk of testicular cancer, which speaks against a causal interpretation of our findings for early exposure to primary air pollution from local sources. Since this is the first study on air pollution and risk of testicular cancer, a comparison with the results of future studies would qualify the interpretation of our findings.

We modeled air pollution, which is inevitable associated with some degree of exposure misclassification. However, the DEHM/UBM/AirGIS air pollution modeling system used in our study has been successfully validated and predicts both temporal and geographical variation in air pollution well (Supplementary Materials and Methods; refs. 41, 50). We would expect that the model predicts air pollution more precisely in the later than in the early period (Supplementary Materials and Methods), but the results for cases diagnosed between 1989 and 1999 were similar to those for cases diagnosed between 2000 and 2014. We were unable to assess air pollution exposure at locations other than the residential address, such as occupational exposure, during commuting or indoors. We would expect the inevitable misclassification to be nondifferential and, therefore, it might have moved the risk estimates towards null.

Our study's major strengths include use of the virtually complete and reliable nation-wide Danish registries providing a nearly perfect frame for case identification, control selection, and identification of present and historical addresses. It was a strength of the study to identify and exclude cases and controls with a history of cryptorchidism, born with congenital malformation of male genitals, and Klinefelter syndrome. These conditions are well-established risk factors for testicular cancer. We cannot exclude that air pollution would affect the risk for testicular cancer differently among those with and without these condition and we excluded individuals with the conditions to avoid their potential influence on our risk estimates. We were also able to restrict our cases and controls to individuals with no prior history of cancer (except nonmelanoma skin cancer); this further minimized risk of bias related to cancer therapy or change in lifestyle after a cancer

Table 2. Outdoor exposure of air pollution given as time-weighted averages over the addresses 10 years prior to index date.

Exposure ($\mu g/m^3$)		Min	5th pctl	Median	95th pctl	Max	IQR	Mean	SD
NO_2	Controls	5.83	11.09	20.52	36.12	76.45	10.80	21.75	8.02
	Cases	5.58	10.97	20.46	36.06	66.87	11.00	21.66	8.09
SO_2	Controls	2.00	3.24	10.93	32.47	50.36	13.70	13.63	9.55
	Cases	2.01	3.18	10.26	32.19	48.72	13.30	13.20	9.51
O_3	Controls	18.69	46.71	59.71	69.34	77.35	9.60	58.99	7.13
	Cases	15.32	46.68	59.81	69.73	76.95	9.88	59.09	7.25
$PM_{2.5}$	Controls	9.51	13.17	17.91	23.83	39.72	5.68	18.20	3.48
	Cases	9.74	13.10	17.55	13.70	35.49	5.67	18.02	3.50
BC	Controls	0.28	0.45	0.77	1.54	6.33	0.41	0.85	0.39
	Cases	0.27	0.45	0.76	1.55	4.57	0.41	0.85	0.39
OC	Controls	0.64	0.93	1.32	2.59	2.92	0.70	1.51	0.52
	Cases	0.65	0.92	1.32	2.61	2.88	0.73	1.51	0.53
SOA	Controls	0.20	0.26	0.31	0.37	0.41	0.05	0.31	0.03
	Cases	0.22	0.26	0.31	0.37	0.39	0.05	0.31	0.03
SIA	Controls	3.39	4.86	8.11	12.41	15.07	4.25	8.34	2.47
	Cases	3.39	4.80	7.87	12.31	14.68	4.24	8.19	2.46
NH_4	Controls	0.37	0.80	1.47	2.47	3.37	0.82	1.52	0.53
	Cases	0.37	0.78	1.42	2.44	3.22	0.82	1.49	0.52
NO_3	Controls	1.89	2.61	3.72	4.86	5.74	1.02	3.71	0.69
	Cases	1.88	2.58	3.67	4.82	5.66	1.04	3.66	0.69
SO_4	Controls	1.14	1.42	2.89	5.39	6.26	2.35	3.11	1.33
	Cases	1.14	1.41	2.74	5.36	6.08	2.33	3.03	1.32
Sea-salt	Controls	2.83	3.30	4.06	5.33	7.64	0.87	4.10	0.64
	Cases	2.83	3.30	4.05	5.38	7.31	0.89	4.10	0.65

Abbreviations: IQR, interquartile range; Max, maximum; Min, minimum; pctl, percentile.

diagnosis. We restricted our study population to individuals born in Denmark, which ensured information about full residential history.

We had no information about individual level factors such as smoking, diet, physical activity, alcohol consumption, body weight, and occupational exposure. None of these, however, are established risk factor for testicular cancer, but should they be risk factors and should they be associated with air pollution as well, then confounding from such factors cannot be excluded. We could not account for family history of testicular cancer, in utero exposure to estrogen, and history of inguinal hernia. *In utero* exposure to estrogen is a rare condition and occurs during unplanned pregnancy when the expecting mother uses oral contraceptive. Oral contraceptive, in a real-life condition of use, it is about 92% effective (51); still, only a small proportion of the few women getting pregnant while using oral contraceptives are likely to

Table 3. Associations[a] between air pollution at the residence during four different time-windows and risk for testicular cancer.

	OR (95% CI)			
Exposure (contrast in $\mu g/m^3$)	The year before birth (660 cases; 1,736 controls)[b]	The first 10 years of life (897 cases; 2,360 controls)[b]	10–20 years before diagnosis (10-year lag; 3,645 cases; 10,354 controls)[b]	The 10 years before diagnosis (6,390 cases; 18,997 controls)
NO_2 (10)	0.87 (0.77–0.97)	0.91 (0.82–1.02)	0.98 (0.92–1.03)	0.99 (0.94–1.04)
SO_2 (10)	0.99 (0.92–1.05)	0.95 (0.85–1.07)	1.03 (0.94–1.12)	0.99 (0.91–1.07)
O_3 (10)	1.04 (0.97–1.11)	1.20 (1.07–1.34)	1.03 (0.97–1.10)	1.01 (0.95–1.07)
$PM_{2.5}$ (5)	0.97 (0.84–1.12)	1.10 (0.89–1.35)	1.04 (0.92–1.17)	0.97 (0.87–1.08)
BC (1)	0.83 (0.67–1.02)	0.84 (0.67–1.06)	0.73 (0.28–1.93)	1.00 (0.91–1.10)
OC (1)	0.84 (0.72–0.98)	0.79 (0.67–0.93)	0.98 (0.90–1.07)	1.04 (0.96–1.12)
SOA (0.1)	0.91 (0.72–1.16)	0.78 (0.36–1.68)	1.05 (0.37–2.99)	1.13 (0.35–3.67)
SIA (1)	1.01 (0.97–1.05)	1.07 (1.00–1.15)	1.02 (0.97–1.06)	0.96 (0.92–1.01)
NH_4 (1)	1.08 (0.92–1.27)	1.25 (0.98–1.59)	1.02 (0.87–1.19)	0.86 (0.74–1.01)
NO_3 (1)	1.03 (0.93–1.13)	1.18 (1.00–1.39)	1.01 (0.91–1.11)	0.93 (0.85–1.03)
SO_4 (1)	1.01 (0.93–1.10)	1.17 (0.96–1.42)	1.11 (0.97–1.28)	0.91 (0.78–1.07)
Sea-salt (1)	1.01 (0.96–1.07)	1.11 (1.00–1.24)	1.01 (0.95–1.07)	1.02 (0.97–1.08)

[a]Adjusted for age and calendar time (1-year categories) by matched design, marital status, personal income, and labor market attachment, and neighborhood level characteristics: manual labor, income, and home ownership.

[b]Numbers differ from the 6,390 cases and 18,997 controls included in the analyses of exposure during the last 10 years before diagnosis. That is because our exposure assessment started in 1979, which left "early" cases without information about exposure. For example, for exposure during the year before birth, participants born prior to 1980 were excluded (5,710 cases; 17,187 controls). In addition, participants with missing exposure more than 20% of the year preceding birth were excluded (20 cases; 74 controls).

Table 4. Associations[a] between air pollution at the residence during the last 10 years before the diagnosis and risk for testicular cancer, by age at diagnosis.

	OR (95% CI)			
Exposure (contrast in $\mu g/m^3$)	Full dataset 6,390 cases; 18,997 controls	Age 35 and below 3,149 cases; 9,250 controls	Age 36 and above 3,241 cases; 9,747 controls	*P* value[b]
NO_2 (10)	0.99 (0.94–1.04)	0.95 (0.89–1.02)	1.03 (0.96–1.11)	0.29
SO_2 (10)	0.99 (0.91–1.07)	0.97 (0.87–1.08)	1.01 (0.90–1.14)	0.72
O_3 (10)	1.01 (0.95–1.07)	1.06 (0.98–1.15)	0.96 (0.89–1.04)	0.33
$PM_{2.5}$ (5)	0.97 (0.87–1.08)	0.98 (0.84–1.13)	0.97 (0.84–1.13)	0.88
BC (1)	1.00 (0.91–1.10)	0.97 (0.85–1.11)	1.04 (0.92–1.17)	0.61
OC (1)	1.04 (0.96–1.12)	0.90 (0.81–1.01)	1.20 (1.07–1.35)	0.05
SOA (0.1)	1.13 (0.35–3.67)	0.38 (0.08–1.76)	2.52 (0.54–11.72)	0.23
SIA (1)	0.96 (0.92–1.01)	0.98 (0.92–1.05)	0.94 (0.88–1.01)	0.45
NH_4 (1)	0.86 (0.74–1.01)	0.89 (0.71–1.12)	0.82 (0.65–1.03)	0.84
NO_3 (1)	0.93 (0.85–1.03)	0.99 (0.86–1.13)	0.88 (0.77–1.01)	0.37
SO_4 (1)	0.91 (0.78–1.07)	0.95 (0.76–1.12)	0.87 (0.69–1.09)	0.43
Sea-salt (1)	1.02 (0.97–1.08)	1.04 (0.96–1.12)	1.00 (0.93–1.08)	0.71

[a]Adjusted for age and calendar time (1-year categories) by matched design, marital status, personal income, and labor market attachment and neighborhood-level characteristics: manual labor, income, and home ownership.
[b]$P_{interaction}$ between air pollution exposure and age.

give birth. Thus, any bias due to this is probably very small. Inguinal hernia can increase testicular cancer risk (52) but in Denmark, all residents have universal, free access to health care, making it unlikely that such operation is associated with air pollution.

Air pollution concentrations in Denmark are relatively low when compared with many other European countries, and not least when compared with many cities in developing countries. We cannot exclude that associations which were undetected in our study, would exist and be detectable in populations exposed to higher air pollution levels.

Conclusion

We found that early life exposure to NO_2 and OC was associated with lower risk for testicular cancer whereas early life exposure to O_3 and SIA was associated with higher risk. Exposure to OC during the last 10 years before diagnosis was associated with higher risk for testicular cancer diagnosed after age 35. These findings might be due to chance and need replication in future studies.

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Authors' Contributions

T. Taj: Data curation, formal analysis, writing–original draft. **A.H. Poulsen:** Data curation, formal analysis, writing–review and editing. **M. Ketzel:** Writing–review and editing. **C. Geels:** Writing–review and editing. **J. Brandt:** Writing–review and editing. **J.H. Christensen:** Writing–review and editing. **U.A. Hvidtfeldt:** Resources, writing–review and editing. **M. Sørensen:** Conceptualization, methodology, writing–review and editing. **O. Raaschou-Nielsen:** Conceptualization, supervision, methodology, writing–review and editing.

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