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Maternal smoking during pregnancy and testicular cancer in the sons: A nested case–control study and a meta-analysis

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ABSTRACT

Some large ecological studies have noted a significant association of testicular cancer (TC) with maternal smoking during pregnancy, while several more controlled studies have been negative. It has been difficult to obtain reliable data on exposure because of the long lag time to cancer diagnosis. We performed a case–control study nested within Finnish, Swedish and Icelandic maternity cohorts exploiting early pregnancy serum samples to evaluate the role of maternal smoking in the risk of TC in the offspring. After reviewing the literature, we also performed a meta-analysis of published studies. For each index mother of the TC patient, three to nine matched control mothers with a cancer-free son born at the same time as the TC case were identified within each cohort. First trimester sera were retrieved from the 70 index mothers and 519 control mothers and were tested for cotinine level by a novel HPLC–MS–MS method developed. No statistically significant association between maternal cotinine level and risk of TC in the offspring was found (OR 0.68; 95% CI 0.35, 1.34). This is the first study based on individual exposure measurements. Its results agree with our meta-analysis of seven previous epidemiological studies (total number of 2149 cases, 2762 controls) using indirect exposure assessment (OR 1.0; 95% CI 0.88, 1.12).

1. Introduction

Incidence of testicular cancer (TC) has been increasing during the last decades in many countries,[1] and it also varies remarkably between countries.[2–4] A variety of factors have been suggested as causes of this cancer, but none explain the increasing incidence. There is a hereditary susceptibility.[5,6] As the tumour typically occurs at early age, major aeti-

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ological factors must operate early in life and possibly already *in utero*.[7,8] Cryptorchidism[9–11] and low birth weight[12,13] are established risk factors of TC. Both cryptorchidism[14,15] and low birth weight[16] have been associated with maternal smoking. TC has been associated with oestrogen treatment[17] or both low and high endogenous oestrogen levels during pregnancy, but these explanations have also been disputed.[18] TC has also been implied as one manifestation of a broader testicular dysgenesis syndrome (TDS) potentially associating with various hormonal and environmental stressors during pregnancy.[19]

Clemmesen[20] noted parallel trends of TC, and female cancers associated with smoking, such as lung cancer and bladder cancer, and this encouraged him to present a hypothesis that maternal smoking during pregnancy is an important risk factor for TC. A similar association was observed in a Swedish study.[21] The hypothesis was put to test in an ecological study from four Nordic countries.[22] There was a highly significant association between female smoking prevalence at 25–29 years of age among 5-year birth cohorts 1910–1940 and TC incidences in 5-year cohorts 28 years later in four Nordic countries pooled. Even within three of the single countries, there was a statistically significant association between female smoking and TC incidence. On the other hand, several studies with sufficient information on exposure, outcome and possible confounding factors did not show such an association.[10,23–28]

Ecological fallacy is an important source of potential error, and we therefore wanted to find a different study strategy to confirm or refute the hypothesis of maternal smoking. There is a unique possibility in the Nordic countries of attempting this. Besides a long tradition of maintaining cancer registries with practically 100% coverage,[29] there is also a maternity care system maintained by the local government (city etc.), including taking blood samples during pregnancy. Participation is a requirement for some economical benefits at childbirth, and therefore the coverage among pregnant women is close to 100%.

The samples obtained from maternity archives were used for cotinine analysis. This metabolite of nicotine is a good indicator of smoking and passive smoking, because its half-life is 14–20 h,[30] much longer than that of nicotine. Even though there are data that the half-life of cotinine may be shorter in pregnant smokers, about 9 h,[31] cotinine still reveals smoking even after 1–2 days' abstinence. Cotinine concentrations were assayed in the present study from the blood samples of mothers of boys with TC and referent mothers of boys born at the same time as the case. Validity of cotinine samples stored up to 20 years has been demonstrated.[32]

The results of the case–control study were compared with existing information by performing a meta-analysis of seven epidemiological studies using smoking information from questionnaires.

2. Material and methods

2.1. Serum banks and cancer registries

Details about Nordic maternity cohorts have been previously reported.[33] In brief, Finnish Maternity Cohort (FMC) of the National Public Health Institute possesses serum samples from almost all pregnant Finnish women (~98%). The blood samples have been collected from women during 10 to 14 weeks of pregnancy following an informed consent for screening of congenital infections. Since 1983, the left-over sample volumes of 1–3 ml of the separated sera have been stored at –25 °C. There is a provision in the Law on the National Public Health Institute that these samples may later be used for scientific studies.

The Northern Sweden Maternity Cohort is based at the Umeå University Hospital, Umeå, including residents of the four northernmost counties of Sweden. Blood samples are drawn from pregnant women during the first trimester or the early weeks of the second trimester (weeks 7–18) as a part of screening for infectious diseases. Since 1975 the serum samples have been stored at –20 °C.

The Rubella Screening Serum Bank at the Department of Virology, University of Iceland, contains serum samples collected since 1980 from more than 95% of pregnant women in Iceland at 12–14 weeks of gestation. The samples are stored at –20 °C.

TC cases were identified in the nationwide Finnish and Icelandic cancer registries and in the regional cancer registry at the Oncological Centre in Umeå that covers the four northernmost counties in Sweden. Cancer registries receive notifications from hospitals, pathology laboratories and physicians, achieving almost 100% reporting coverage. Cancer registries in Finland and Iceland also utilise death certificate information as an additional source of information.

Over-generation linkage (son–mother) of the population census registry, cancer registry and the maternity cohort data enabled identification of women with offspring who have been diagnosed with testicular cancer. Permission for linkage information between Finnish Maternity Cohort, Population Registry and Cancer Registry has been obtained from the Ministry of Health and the Population Census Register of Finland (#1422/54/94). Relevant permissions were obtained from the Icelandic National Bioethics Committee (#03-013) and the Icelandic Data Protection Authority (#2003/308). Similar approvals were also available in Sweden from research ethical committees.

Research protocol of this study was accepted by the Institutional Review Board of the Finnish National Public Health Institute (7/2006).

2.2. Study subjects

The study was conducted as a pair-matched case–control study nested within Finnish, Swedish and Icelandic maternity cohorts. TC cases diagnosed between 1985 and 2003, between 1976 and 2006 and between 1979 and 2006 were identified from the Finnish, Swedish and Icelandic cancer registries, respectively. Initially 68 TC cases in Finland, 34 TC cases in Northern Sweden and 13 TC cases in Iceland were diagnosed with a histologically verified testicular germ cell tumour (including embryonal carcinoma, seminoma, teratoma and other histological types). Altogether 45 TC cases were excluded from the study. The main reasons for exclusion were absence of maternal serum sample in one of the maternity cohorts (36 cases), or that the pregnancy took place before