Is Pregnancy Smoking Causal to Testis Cancer in Sons?

A Hypothesis

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Inquiry studies into smoking during pregnancy as a possible cause of testis cancer in sons are found misinterpreted as purely negative. Danish quinquennial incidence rates for patients aged 25–39 years are compared with rates for tobacco-induced neoplasms among the corresponding maternal generation, primarily of bladder tumours including papillomas, and of lung—both for ages 50–64 years, allowing for period of latency. Corresponding to a delay of increase, earlier demonstrated for incidence rates of testis cancer among men born 1939–1945, delays of increase are found for female bladder and lung with allowance for lag-times of 30 and 20 years respectively. Comparison of data from Scandinavian nationwide cancer registries show a noteworthy parallelism of trends from first to last plotting of testis/female bladder ratios. The rise for lung is found steeper in consequence of age distribution.

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The increase in incidence of testicular cancer in Western countries during the last decades was first observed in Denmark, showing the highest rates on record for Copenhagen with suburbs (1–4). International differences are largely determined by a characteristic culmination of incidence rates between 25 and 49 years of age, while a modest rise for older age groups varies but little between countries.

Like other neoplasms testicular cancer has been ascribed to a variety of causes, none of which well established, except a limited hereditary trend (5), and the reason may well be an interaction of causative factors. Some recent discussion has centered on an effect from high maternal oestrogen level during pregnancy (6), but also the suggestion of maternal smoking seems worthy of reconsideration as a contributary factor. A few authors have examined if the culmination of incidence rates for testicular cancer below 50 years of age might be due to maternal smoking during pregnancy, but results from their difficult inquiries into prenatal smoking habits of mothers of patients have, mostly but unjustified, been interpreted as purely negative.

A study in Los Angeles (7) covering a total of 178 patients with testis cancer, aged 15 to 40 years, reported on smoking among 79 live mothers of patients, and 79 control mothers, while an English study from the West Midlands (8) covered 469 testis cancer cases, aged from 10 up to 60 years, and succeeded to interview 259 cases with two control groups of 238 and 251 women. Neither study found difference in tobacco consumption between patients' mothers for which information was available, and control mothers, but causes of the not inconsiderable number of intervening deaths were not accounted for.

The significance of this item appears from a study series in Washington DC (9) covering 308 testis cancer survivors out of 335 patients, allowing telephone interviews of 225 mothers and 213 control mothers.

It should be noted that this study, of patients aged between 18 and 42 years, found low birth weight the feature strongest associated with testicular cancer, like also constantly reported for births by smoking women (10).

Furthermore, the Washington study showed the risk of testis cancer in sons, born of mothers smoking up to 40 cigarettes daily 1.5 times the risk for controls. However, the apparent absence of this risk at higher consumption prevented authors from concluding to a relationship consistent with amounts smoked, although not irreconcilable with an effect. Also for this study the essential question remains of the causes of deaths among mothers smoking more than 40 cigarettes daily, during the 18 to 42 years until testis cancer was diagnosed with their sons.

DANISH DATA

Incidence data of the present study originate with nationwide cancer registries, mostly the Danish, organised by

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the author in 1942. The reliability of registry data was recently internationally reviewed (11).

The comparison of the top rates for testicular cancer in Copenhagen and suburbs with local rates for tobacco cancers has been based on previous analyses of local data for bladder tumours including premalignant cases. Patients from Copenhagen 1956–1959 were questioned in detail with a view to causation, and, in the absence of any association with occupation or drugs, data were particularly suited for analysis of the effect from tobacco (12, 13). The age curve of lung cancer (14), determined by the coaction of carcinogens in air as well as in blood, would naturally take a steeper course, less comparable with the age curve for the testis, than the curve for bladder tumours.

Up to World War II, cigars made a major part of Danish tobacco consumption, and a decrease during wartime, although partly regained, was after the war replaced by a steeper increase in the sale of cigarettes (14). This applied not least to women, followed in due course by rising rates for lung cancer and bladder tumours (13, 15). Anti-smoking campaigns, begun in 1952, proved less effective than elsewhere (16), and least among women. For both sexes, however, smokers of more than 15 cigarettes per day, tended to cover an increasing part (17).

An epidemiological comparison from 1992 by the University of Aarhus (18) reported 41% of Danish women smoking, against 33% in Norway, 25% in Sweden, and 20% in Finland. For women aged over 15 years, the percentage of everyday smokers, ranking highest within the European Union, with about 42% including the pregnant and 30% on delivery (18, 19), leaving undefined the period of pregnancy subject to particular risk.

In the present context it seems essential that the percentage of smokers of more than 15 cigarettes per day (17) increased among both sexes, despite a slight general trend of decrease.

In 1989, H. Møller published the significant observation of a delay in the increase of testis cancer in Denmark due to a decrease in cases born 1940–1945 during World War II (20), and as shown in Table 1 for Copenhagen this applies to the three quinquennial groups aged 25 to 39 years. Among the possible explanations offered by the author the only one tenable from later data is the well-documented decrease in tobacco consumption during wartime (15, 20), when Denmark was among the few European nations without essential impairment of food consumption. In fact, rations were cut following the German capitulation in 1945.

METHODS

An overall measure of the cancer risk to embryos from mothers' smoking during pregnancy may be found in the incidence of tobacco-induced cancers among women, with allowance for an average lag-time of 25 years for lung and bladder, and referring to groups aged 50 to 64 years at diagnosis. In Copenhagen, the specific latent period for bladder, including papillomas, has been estimated at about 30 years, against 20 years for bronchial carcinoma (15), although clearly with less accuracy than expected from an exposure limited to pregnancy.

Thus, the age curve for bladder tumours will be more comparable in level and shape with the early curve of testis cancer, despite being placed 10 years later in life than the curve for lung cancer, with its combined exposure to air-borne and blood-borne carcinogens.

Table 1

Testis cancer, per 100 000. Greater Copenhagen 1943–1987

	Age at registration by year of birth.		
	25–29 years	30–34 years	35–39 years
Born			
1914–22	5.9	11.0	9.9
1919–27	8.3	9.5	13.1
1924–32	10.9	15.3	13.5
1929–37	14.5	17.4	23.3
1934–42	13.2	13.7	21.5
1939–47	13.1	16.0	19.2
1944–52	17.9	20.2	20.4

RESULTS

From the time-pattern of Table 1 it appears, that with one exception all periods showing a decrease in Danish rates of testis cancer include cases born 1939–1945.

Table 2 shows rates for testis cancer cases in greater Copenhagen aged 25–39 years, correlated with corresponding rates for female bladder tumours, including papillomas, with allowance for an average lag-time of 25 years, and aged 50 to 64 years.

A fortuitous similarity in numbers and rates facilitates comparison of cancer data between testis and bladder of the maternal generation about 25 years after births of their sons.

With a view to its trend of shorter latency, data for lung cancer are also presented for the age group 40–54 years, showing a corresponding effect.

It appears that the temporary delay in increase (indicated vertically in Fig. 1) for testis cases born 1939–1945 coincides with a delay of the rates for female bladder, (horizontally plotted in Fig. 1) and for lung about 10 years earlier at 10 years younger age, all according to the respective lagtimes.

For an estimate of corresponding causal factors in countries of more moderate rates for testicular cancer, advantage has been taken from incidence data published by the international Union Against Cancer, by the International Agency for Cancer Research, and by Scandinavian cancer registries (21–24). Data covering several decades of com-

Table 2

Greater Copenhagen (capital with suburbs) 1943 1987. Delays in increase of cancer incidence per 100 000 for 15-year age groups

Aged		Males	Females		
		Testis 25–39 years	Bladder 50–64 years	Lung 40–54 years	50–64 years
Born	Diagnosed				
1904–22	1943–47	6.3	7.8	17.9	12.0
1909–27	1948–52	8.3	10.3	*28.0*	*18.0*
1914–32	1953–57	9.7	11.1	*25.8*	*17.7*
1919–37	1958–62	*14.2*	*13.7*	38.5	23.5
1924–42	1963–67	*14.7*	*13.3*	68.2	32.0
1929–47	1968–72	16.1	17.5	79.1	43.6
1934–52	1973–77	17.6	21.0	132.6	59.4
1939–51	1978–82	21.4	23.3	158.5	80.0
1944–62	1983–87	23.8	24.9	235.5	126.1

parable adequate registration come from the nationwide registries of five Nordic countries and New Zealand supplemented with rates from the oldest regional registry—of Connecticut.

The figure shows rates for testis cancer cases aged 25–39 years plotted vertically against horizontal plottings for female bladder cases aged 50–64 years. It may be noted that levels for Scandinavian countries correspond in sequence to their national percentages of women smoking (16).

In straightness the Danish graph, with its single irregularity affecting both sites of cancer for World War II, is surpassed only by Finland's at a far lower level for both sites, in contradistinction to its Scandinavian top-rate for male lung cancer (14).

Naturally, nationwide registration will offer better possibilities for follow-up of patients than a regional system of similar coverage. Still, both Norway and Connecticut show irregularities of graphs, explainable from reported changes of histological criteria of bladder papilloma.

A feature more dominant than such temporary inconsistencies would appear from lines drawn from first to last plottings of the Scandinavian and New Zealand data. It would display an overall prallelism of trends, indicating consistency of testis/bladder ratios for the age groups concerned, and thus strongly suggesting similarity of causation.

Contrarily, it will be expected that a graph from some larger country, e.g. covering a region dominated by dyestuff industry, may display an excess of bladder cancer cases. Closer analysis of such data may well yield valuable information on the coaction of causative factors, while present evidence seems adequate for the warning of pregnant women against smoking.

DISCUSSION

Since the demonstration of an increase in frequency of testicular cancer in Western countries (3), only few suggestions of its causation have proved convincing such as of a modest hereditary trend (5). Recent hypotheses have suggested a causal effect from hormones, originally referring to oestrogens, but later extended to the notion of xenoestrogens with similar effect, suspected from food additives, contaminants, packing or wrapping materials, and pollutants of air and water, etc.

In support of this hypothesis an international workshop (6) has pointed to coincidence in time of an increase in frequency of some congenital malformations, like hypospadia, "postulating" a higher incidence of chryptorchism in Denmark than in Finland with rising prevalence of genital malformations among newborns.

It should, however, be noted that the workshop's diagrams on Nordic national incidence rates show different sequences for hypospadia and for testis cancer. While hypospadia rates for Sweden take the first position followed by Norway, Denmark and Finland, rates of testis cancer in Sweden take the third position in exchange with Denmark in the first place. No explanation is offered of the incompatibility of this difference with the assumption of a common causation, and, contrarily, it may be noticed that the hypothesis of a prenatal effect from the carcinogenic potency of tobacco products meets with no such incongruence of incidence data. In fact, the hypothesis of maternal smoking as a cause of testicular cancer is well in keeping with the observation of low birth weight following pregnancy smoking (9) and preceding testicular cancer as well (8).

In the absence of noticeable occupational risks of bladder tumours in Copenhagen (12) their local incidence rates will make a more applicable measure of cancer risk from tobacco, than does the incidence of lung cancer (13–15), ascribable to carcinogens from inhalation as well as from blood. In the causation of testis cancer, tobacco will be worthy of note already in consideration of its temporary decrease in risk for Wartimeborn male babies, and the

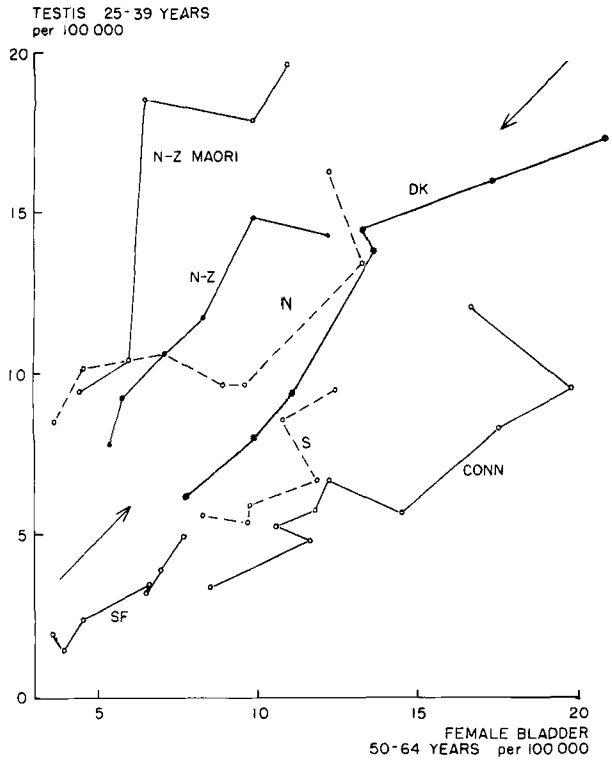

Figure. Development in ratios of incidence rates for testis to rates for female bladder tumours:
Data from Cancer Registries, 1940–90.
N–Z Maori: New Zealand Maoris 1960–62 to 1983–87
N–Z: New Zealand Non-Maoris 1960–62 to 1983–87
DK: Denmark: Copenhagen 1943–47 to 1973–77
N: Norway: 1959–61 to 1981–85
S: Sweden: 1959–61 to 1981–85
SF: Finland: 1959–61 to 1986–90
Connecticut: 1940–44 to 1983–87
Incidence rates per 100 000 for testicular carcinoma at age 25–39 years, plotted vertically against female (maternal) risk of bladder tumours per 100 000 at 50–64 years, horizontally plotted. Arrows indicate the level of ratio 1:1.
All graphs, except for Maoris, display a parallel overall trend from first to last plotting. Closest to a linear course is the Finland graph while the Danish shows but one striking deviation, between 1958–62 and 1963–67, corresponding to the wartime smoking deficit in Copenhagen cf. Tables. Cf. text about the similar graphs of Norway and Connecticut.

corresponding delays of increase in mothers' rates of neoplasms in bladder and lung, in accordance with local lagtimes. To this come international top rates for testicular cancer on the background of persistent local numbers of heavy smokers during pregnancy (17).

The topical hypothesis of an effect from hormonal therapy, causing increasing congenital malformations and cases of testicular cancer in childhood (6), may raise suspicion of a similar effect from possible xenoestrogens among tobacco products, and support earlier suggestions of a possible effect on the genome (26–29) from tobacco. It seems worth the while to emphasize, that the tobacco hypothesis in contradistinction to the vaguer concept of xenoestrogens provides a working hypothesis directly applicable for prevention.

Epidemiology taking issue from clinical observation, often has to produce its final proof by elimination of a suspected causal fator, while statistical estimate or risks may take decades for convincing about the part it plays, perhaps within a pattern of carcinogens (15–29).

For the time being, it may be realized that interviews with mothers of testis cancer patients may be more successful if taken directly by physicians, than by their clerks on telephone. A final rational answer may best be provided by registration of smoking habits and hormonal dosage of pregnant women with birth dates and names of their sons noted for later follow-up. In the meantime, the drawbacks from advice against smoking in pregnancy seem tolerable.

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