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ORIGINAL RESEARCH

Having children with multiple partners is associated with reduced risk of malignant melanoma: an observation seeking a plausible explanation

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Objective: We examined the association between the number of partners that mothers and fathers have children with and occurrence of cutaneous malignant melanoma (CMM).

Methods: We conducted a complete registry-based follow-up of all Danish mothers born after 1935 from the birth of their second child until CMM, death, emigration, or end of study in 2002. We conducted a similar follow-up of the corresponding fathers. Incidence rate ratios (IRR) and confidence intervals (CI) were estimated by Poisson regression.

Results: This study corroborates that women having children with three or more men are half as likely to have CMM as women who have children with one man: incidence rate ratio (IRR) = 0.51, 95% CI: 0.29, 0.91; having children by two fathers reduces risk among women by 20%: IRR = 0.80, 95% CI: 0.70, 0.91. Fathers with multiple partners tend to face a similar risk reduction.

Conclusion: The similar patterns of mothers and fathers challenge us to consider and propose likely mechanisms common to both sexes. The patterns of reduced risk have now been reported in two large independent complete population-based studies in Sweden and Denmark.

Keywords: malignant melanoma, epidemiology, children with multiple partners

Introduction

Women who bear children of different men have a reduced risk of cutaneous malignant melanoma (CMM).[1,2] The unraveling of the etiology of CMM has focused on sun exposure, skin sensitivity, and genetics. Reproductive factors may also influence the risk of CMM in younger mothers[3–6] through acquisition from the child's father of protective stem cells, as suggested by the fetal antigen hypothesis.[7,8] Thus, having children fathered by multiple men seems to "vaccinate" women against CMM, but no similar mechanism is present in men.

Recently, Campi et al[1] reported that Danish women having children with different men had an almost halved risk of CMM compared with women with no change of partner. This study was based on data from 1.6 million women-years at risk and 245 CMM cases. Similar findings were reported by Li and Hemminki in Sweden,[2,9] who also found a reduced risk of CMM for men who fathered children with different women. The objective of this study is to update the finding in Denmark[1] with more recent data and longer follow-up, while supplementing the findings with Danish data on fathers.

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Materials and methods

We conducted this nationwide follow-up study using data from administrative and medical registries in Denmark.[10]

Using Denmark's Civil Registration System (CRS), we identified all women born after 1935 who were alive on April 2, 1968. Those dates were chosen in order to maximize the time available for identification of linkage between the mother and her children. The CRS, established on April 2, 1968, includes all Danish citizens who were alive on or born after that date. Similarly, we used CRS to establish the cohort of fathers alive on April 2, 1968. Follow-up of mothers and fathers continued from the birth of their second child until CMM diagnosis, death, emigration, or the end of the study, on December 31, 2002.

Incident cases of CMM among the mothers and the fathers were identified from the Danish Cancer Registry.[11] We estimated the incidence rate ratio (IRR) by Poisson regression, using STATA 10 statistical software (StataCorp LP, College Station, TX).

Exposure started at the birth of the first child whose father or mother was different from the one registered at the previous birth(s) (by number of different fathers/mothers: 1, 2, and 3+). We considered women and men "exposed" if they had at least one child by a different partner than their first child, that is, if at least two different identifiable fathers or mothers were registered. Women who had a missing identifier for the father and no indication of a different father in any of the pregnancies were considered unexposed. Some of the offspring could not be linked to a father if the father either died before April 2, 1968, or if he was too old to be identifiable in the CRS; implying that some of the older fathers dropped out, or could be misclassified as having fewer partners than they actually did. By design, all mothers were known. The variables for potential confounders were derived from the CRS. Potential confounders included current parental age (in groups: <29, 30–39, 40–49, 50–59, and 60–69 years); current calendar period (in five categories: 1935–64, 1965–74, 1975–84, 1985–94, and 1995–2002); time since last birth (dichotomous: <10 or >10 years); parity (2, 3, 4, 5, ≥6, defining parity of both fathers and mothers as the number of registered live-born children); and the mother's or father's age at first birth (in groups: <24, 25–29, 30–34, and ≥35 years).

Results

Among 941,228 women giving birth to two or more children in the period from 1950 to 2002, we identified 3,687 with incident CMM during 19.7 million women-years at risk. Among the women included in this study only 1.6% had partners with missing identity. A total of 899,942 fathers of known identity were eligible for follow-up from the birth of their second child; among them, we identified 2,837 cases of CMM during 18.5 million men-years. Tables 1 and 2 show IRRs for the association between the number of births resulting from different partners and subsequent risk of CMM, estimated by Poisson regression. We present these results separately for women (Table 1) and men (Table 2).

Women who had children fathered by two men had a 20% reduction in the CMM risk compared with women who had children with one man: incidence rate ratio (IRR) = 0.80, 95% confidence interval (CI): 0.70, 0.91, $P = 0.001$; the risk was halved among women whose children were fathered by three or more men: IRR = 0.51, 95% CI: 0.29, 0.91, $P = 0.03$. Among men who had children with two or more different women reduction of risk was similar to that of women with analogous reproductive history. Compared with men who had children with one woman, IRR of CMM was 0.87, 95% CI: 0.75, 1.01, $P = 0.07$ for men who fathered children with two different women; for men who fathered children with three or more women: IRR = 0.68, 95% CI: 0.40, 1.14, $P = 0.14$. With the purpose of providing data for use in power calculations of future studies, we have added estimates of all IRRs in the used multivariate model (Tables 1 and 2).

Discussion

Both women and men who had children with more than one partner had a lower risk of CMM than their counterparts having children with one partner. The results reached statistical significance at the 5% level only for women. However, the dose-response pattern, observed among both women and men, is evidence against these findings occurring by chance. The fetal antigen hypothesis might be an interesting explanation of the finding in females, but it does not explain the similar findings that we see for males.

Our findings are in agreement with results of two Swedish studies for both women[2] and men.[9] Li and Hemminki[2,9] adjusted their estimates for socioeconomic status measured by the six-category variable describing occupation type (agriculture, manual worker, blue collar, professional, self-employed, and others) with information, taken from population censuses held in 1960, 1970, and 1980, applied to the study period from 1961–1980.[12] This variable is probably a crude measure of the true socioeconomic condition, which may explain the similarity of results before and after adjustment for this variable in the two Swedish studies; suggesting that confounding by social conditions, as determined by

Table 1 Incidence rates (IR) of cutaneous malignant melanoma and mutually adjusted incidence rate ratios (IRR) estimated with data from follow-up of Danish mothers from the birth of their second child in the period from 1950 to 2002

	Cases n	Women-years in 100,000s	IR per 100,000	95% CI	Mutually adjusted IRR	95% CI
Total	3,687	196.76	18.7	18.1, 19.4		
1 father	3,419	177.84	19.2	18.6, 19.9	1.00	Ref
2 fathers	256	17.54	14.6	12.9, 16.5	0.80	0.70, 0.91
3+ fathers	12	1.39	8.6	4.9, 15.2	0.51	0.29, 0.91
Mother's age at first birth						
<24	2,422	144.50	16.8	16.1, 17.4	1.00	Ref
25–29	1,032	44.33	23.3	21.9, 24.7	1.20	1.11, 1.30
30–34	205	7.13	28.8	25.1, 33.0	1.36	1.17, 1.58
35+	28	0.81	34.6	23.9, 50.1	1.45	0.99, 2.13
Time since latest birth						
less than 10 years	1,266	100.14	12.6	12.0, 13.4	1.00	Ref
more than 10 years ago	2,421	96.62	25.1	24.1, 26.1	1.09	0.98, 1.21
Age during follow-up						
<29	178	28.95	6.1	5.3, 7.1	1.00	Ref
30–39	1,011	73.65	13.7	12.9, 14.6	1.64	1.38, 1.94
40–49	1,359	56.99	23.8	22.6, 25.2	2.38	1.96, 2.89
50–59	912	31.04	29.4	27.5, 31.4	2.67	2.17, 3.30
60–69	227	6.14	37.0	32.5, 42.1	3.21	2.51, 4.09
70+						
Calendar period during follow-up						
1935–64	7	2.53	2.8	1.3, 5.8	0.27	0.13, 0.57
1965–74	113	20.93	5.4	4.5, 6.5	0.39	0.32, 0.48
1975–84	551	44.38	12.4	11.4, 13.5	0.67	0.60, 0.74
1985–94	1,292	63.50	20.3	19.3, 21.5	0.87	0.81, 0.94
1995–2002	1,724	65.42	26.4	25.1, 27.6	1.00	Ref
Parity						
2	2,458	129.29	19.0	18.3, 19.8	1.00	Ref
3	978	51.27	19.1	17.9, 20.3	0.97	0.90, 1.05
4	208	12.61	16.5	14.4, 18.9	0.84	0.73, 0.97
5	35	2.68	13.1	9.4, 18.2	0.67	0.48, 0.94
6+	8	0.91	8.7	4.4, 17.5	0.44	0.22, 0.89

Notes: Cohort comprised all Danish women born after 1935 and alive on April 2, 1968.

occupation alone, is an insufficient explanation of the findings.

The observed association of reduced risk of melanoma for men and women having children with multiple partners might be due to confounding, not only by socioeconomic conditions. We lack registry data on strong risk factors such as sun exposure and phenotypic characteristics, and uncontrolled confounding could be a possible explanation that should be considered when such risk factors are strongly linked with partner change.

We found, among women and men, mutually adjusted negative associations of both parity and number of the partners with the risk of CMM. Currently, the prevailing explanation of the inverse association between high parity and melanoma risk is almost exclusively related to confounding by lifestyle and socioeconomic status.[2,5,9,12,13] The argument behind this conjecture is that having more children reduces resources needed to obtain excessive sun exposure (eg, leisure time and money), thereby lowering risk of CMM.[5] Similarly, changes of partner may lead to extension of the reproductive period, and result in greater number of children per parent. As a result, the CMM risk among the "partner-changers" decreases secondary to paucity of time and financial resources available for sunbathing. To our knowledge, neither this study nor others present data adequately supporting this explanation of an interplay between number of children, level of sunbathing, and CMM risk. On the contrary, sunbathing could be positively related with family size and multiple partners.

According to a hypothesis introduced by Li and Hemminki,[2] female divorcees have an excess of tobacco-, alcohol- and HPV-related cancers (all of which may be

Table 2 Incidence rates (IR) of cutaneous malignant melanoma and mutually adjusted incidence rate ratios (IRR) estimated with data from follow-up of men that have fathered the offspring of the cohort Danish mothers in Table 1

	Cases n	Men-years in 100,000s	IR per 100,000	95% CI	Mutually adjusted IRR	95% CI
Total	2,837	184.80	15.4	14.8, 15.9		
1 mother	2,610	167.11	15.6	15.0, 16.2	1.00	Ref
2 mothers	212	16.14	13.1	11.5, 15.0	0.87	0.75, 1.01
3+ mothers	15	1.54	9.7	5.9, 16.2	0.68	0.40, 1.14
Father's age at first birth						
<24	1,032	82.29	12.5	11.8, 13.3	1.00	Ref
25–29	1,225	73.19	16.7	15.8, 17.7	1.15	1.06, 1.25
30–34	425	22.60	18.8	17.1, 20.7	1.15	1.02, 1.30
35+	155	6.70	23.1	19.8, 27.1	1.17	0.97, 1.41
Time since latest birth						
less than 10 years	780	93.87	8.3	7.7, 8.9	1.00	Ref
more than 10 years ago	2,057	90.93	22.6	21.7, 23.6	1.18	1.03, 1.34
Age during follow-up						
<29	37	14.27	2.6	1.9, 3.6	1.00	Ref
30–39	489	63.62	7.7	7.0, 8.4	2.17	1.54, 3.06
40–49	881	59.13	14.9	13.9, 15.9	3.33	2.33, 4.75
50–59	958	35.54	27.0	25.3, 28.7	5.03	3.48, 7.27
60–69	414	11.18	37.0	33.6, 40.8	6.15	4.19, 9.02
70+	58	1.06	54.8	42.4, 70.9	8.55	5.35, 13.66
Calendar period during follow-up						
1935–64	4	2.32	1.7	0.6, 4.6	0.21	0.08, 0.57
1965–74	76	19.89	3.8	3.1, 4.8	0.35	0.27, 0.45
1975–84	354	42.40	8.3	7.5, 9.3	0.55	0.48, 0.62
1985–94	899	59.77	15.0	14.1, 16.1	0.72	0.66, 0.79
1995–2002	1,504	60.42	24.9	23.7, 26.2	1.00	Ref
Parity						
2	1,828	120.42	15.2	14.5, 15.9	1.00	Ref
3	749	48.29	15.5	14.4, 16.7	0.93	0.85, 1.01
4	207	12.35	16.8	14.6, 19.2	0.96	0.83, 1.12
5	47	2.77	17.0	12.8, 22.6	0.96	0.71, 1.29
6+	6	0.97	6.2	2.8, 13.7	0.34	0.15, 0.75

Notes: Fathers were followed up from the birth of their second child in the period from 1950 to 2002.

poverty-related), accompanied by lower rates of malignancies related to affluence. For example, Sigvardsson and colleagues[14] reported a decreased risk of CMM in Swedish female alcoholics, while Freedman and colleagues[15] found that long duration of smoking was inversely associated with risk of CMM. The latter study, contrary to expectation, found alcohol intake to be associated with an increased CMM risk, while parity was not associated with it.

In order to encircle the characteristics of a "partner changer", we included the very limited information on maternal socioeconomic conditions in the period from 1980 to 2002. The number of CMM cases was limited between 1980 and 2002, and did not allow for confounder control. As an alternative, we investigated the associations between partner change and socioeconomic condition of the mother of each 1,278,205 births in the period. For each available social status variable, we noticed dose-response relations by partner change (0, 1, 2, 3+ changes); more single mothers (7%, 18%, 31%, 41%), more with no qualifying education (40%, 56%, 74%, 85%), more pensioners and economically inactive women (19%, 29%, 47%, 65%), belonging to the lowest quintile of gross income (19%, 27%, 44%, 64%), and slightly more mothers living outside the capital (68%, 68%, 71%, 75%). Our examination of the associations between partner change and maternal socioeconomic status clearly showed that having children with different men is associated with lower maternal social class. The study can be used as evidence in favor of a relatively strong association between low socioeconomic status and reduced risk of malignant melanoma – at least in women.

Given the contradictory nature of the cited evidence, and the findings that men fathering children with different

partners also had reduced CMM risk, challenge us to consider alternative pathways to CMM. For example, pathways that are related to fecundity and sexual behavior, perhaps of a genetic nature. We recommend new studies that add new putative risk factors to our limited understanding of the etiology of CMM.

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Disclosure

The authors report no conflicts of interest in this work.

References

1. Campi R, Frydenberg M, Basso O, Ebbesen P, Olsen J. Having children with different men and subsequent cancer risk. A nationwide study in Denmark. *Br J Cancer*. 2004;90(7):1374–1377.
2. Li X, Hemminki K. Cancer risks in women who had children with different partners from the Swedish Family-Cancer Database. *Eur J Cancer Prev*. 2002;11(5):433–438.
3. Lens M, Bataille V. Melanoma in relation to reproductive and hormonal factors in women: current review on controversial issues. *Cancer Causes Control*. 2008;19(5):437–442.
4. Neale RE, Darlington S, Murphy MF, Silcocks PB, Purdie DM, Talback M. The effects of twins, parity, and age at first birth on cancer risk in Swedish women. *Twin Res Hum Genet*. 2005;8(2):156–162.
5. Kaae J, Andersen A, Boyd HA, Wohlfahrt, Melbye M. Reproductive history and cutaneous malignant melanoma: a comparison between women and men. *Am J Epidemiol*. 2007;165(11):1265–1270.
6. Lambe M, Thorn M, Sparen P, Bergstrom R, Adami HO. Malignant melanoma: reduced risk associated with early childbearing and multiparity. *Melanoma Res*. 1996;6(2):147–153.
7. Janerich DT. The fetal antigen hypothesis for breast cancer, revisited. *Medical Hypotheses*. 1994;43(2):105–110.
8. Janerich DT, Thompson D. Reduced breast cancer risk after remarriage: evidence of genetic-immune protection. *Epidemiology*. 1995;6(3):254–257.
9. Li X, Hemminki K. Cancer risks in men who had children with different partners from the Swedish Family-Cancer Database. *Eur J Cancer Prev*. 2003;12(5):355–358.
10. Pedersen CB, Gøtzsche H, Møller JO, Mortensen PB. The Danish Civil Registration System. *Dan Med Bull*. 2006;53(4):441–449.
11. Storm HH, Michelsen EV, Clemmensen IH, Pihl J. The Danish Cancer Registry – history, content, quality, and use. *Dan Med Bull*. 1997;44(5):535–539.
12. Hemminki K, Zhang H, Czene K. Socioeconomic factors in cancer in Sweden. *Int J Cancer*. 2003;105(5):692–700.
13. Dalton SO, Schuz J, Engholm G, et al. Social inequality in incidence of and survival from cancer in a population-based study in Denmark, 1994–2003: summary of findings. *Eur J Cancer*. 2008;44(14):2074–2085.
14. Sigvardsson S, Hardell L, Przybeck TR, Cloninger R. Increased risk among Swedish female alcoholics. *Epidemiology*. 1996;7(2):140–143.
15. Freedman MD, Sigurdson A, Doody MM, Rao RS, Linet MS. Risk of melanoma in relation to smoking, alcohol intake, and other factors in a large occupational cohort. *Cancer Causes Control*. 2003;14(5):847–857.