Birth weight and melanoma risk: a population-based case–control study

I Franco-Lie*,1, T Iversen2, TE Robsahm3 and M Abdelnoor4

1Department for Research and Education, Center for Clinical Research, Ulleval University Hospital, Oslo 0407, Norway; 2Department of Oncology, The Norwegian Radium Hospital, Montebello, Oslo 0310, Norway; 3Cancer Registry of Norway, Montebello, Oslo 0310, Norway; 4Section for Epidemiology and Biostatistics, Department for Research and Education, Center for Clinical Research, Ulleval University Hospital, Oslo 0407, Norway

We investigated whether lower birth weight was associated with lower risk of melanoma later in life. This population-based case–control study included all incident cases of histologically verified invasive melanoma diagnosed until 31 December 2003 in the Norwegian population born between 1967 and 1986 (n = 709). The control group without malignant disease was established by random sampling from the same source population as the cases (n = 108 209). Data on birth weight, gender, mother’s residence and parental age at the time of birth were collected from the Medical Birth Registry of Norway and data on cancer from the Cancer Registry of Norway. The Mantel–Haenszel test of linear trend showed no trend in risk across the birth weight categories: individuals in the highest quartile of birth weight (≥3860 g) had an odds ratio (OR) of 1.19 (95% confidence interval, CI: 0.77–1.84) compared to individuals with birth weight <2500 g. The adjusted OR was 0.81 (95% CI: 0.52–1.26) for birth weight below 2500 g (exposed). Though not statistically significant, the results suggest that low birth weight might influence the risk of melanoma later in life.

British Journal of Cancer (2008) 98, 179–182. doi:10.1038/sj.bjc.6604159 www.bjcancer.com

Keywords: melanoma; birth weight; population-based; case–control study

Exposure to intermittent high-dose ultraviolet (UV) radiation is widely recognised as the major cause of cutaneous malignant melanoma (hence referred to as melanoma). In two previous studies, we observed a lower incidence of melanoma in twins as compared to singletons (Iversen et al, 2001; Franco-Lie et al, 2005) as have others (Hemminki and Li, 2002; Hemminki and Chen, 2005; Neale et al, 2005), but for which no biological explanation is evident.

Twins and singletons differ in mean birth weight, length at birth and average duration of gestation. In the United States, mean birth weight is 3531 grams (g) for singletons and 2367 g for twins (Alexander et al, 1998), and Norwegian data are similar.

It has been hypothesised that birth weight can influence the cancer risk later in life. This possible association has been studied for melanoma (Andersson et al, 2001; McCormack et al, 2005; Ahlgren et al, 2007) and other types of cancer (Le Marchand et al, 1988; Tibblin et al, 1995; Roman et al, 1997; Wanderås et al, 1998; Vatten et al, 2002; Hjalgrim et al, 2004; Nilsen et al, 2005; Michos et al, 2007). The results are inconclusive; however, there seems to be an association between birth weight and the risk for some cancer forms.

We investigated whether lower birth weight is related to lower risk of melanoma later in life by estimating the association between birth weight and the incidence of melanoma in the Norwegian population.

MATERIALS AND METHODS

This population-based study includes all live-born men and women (n = 1 142 635) in Norway between 1 January 1967 and 31 December 1986. From this 20-year cohort, a case–control study was carried out.

All incident cases of melanoma diagnosed in that population before 31 December 2003 were identified (n = 859). Melanoma was defined according to the international classification of diseases, and only cases with histologically verified invasive melanoma of primary tumour were included in the study (n = 711). The control group is a random sample of the population, without a malignant disease, born in the same period of time as the cases and in which the individuals were all alive at the closing date 31 December 2003 (n = 109 727).

For all the individuals, data on birth weight, gender, mother’s residence and parental age at the time of birth, maternal pregnancy factors and twin status were collected from the Medical Birth Registry of Norway (MBRN). This is a population-based registry based on compulsory notification of every birth or late abortion with a gestational age of 16 weeks or more. Infants and parents can be identified thorough the national 11-digit personal identification number (Irgens, 2000).

Data on cancer were collected by linkage to the Cancer Registry of Norway, using the unique 11-digit identification number. The cancer registry is population-based (Cancer in Norway, 2006).
Cases without histological verification of the primary tumour ($n = 87$) and cases of multiple cancers ($n = 61$) were excluded from the analyses. Individuals lost to follow-up (controls, $n = 3$) and individuals with follow-up shorter than 1 year (due to emigration or death) were also excluded (case, $n = 1$; controls, $n = 1324$). This 1-year limit was based on the definition of infant mortality rate (Gowen, 2006). Furthermore, individuals with missing data on birth weight (case, $n = 1$; controls, $n = 191$) were also excluded. The final study population includes 709 cases of melanoma and 108209 controls without a malignant disease.

The birth weight (g) was analysed both as a continuous variable and as a categorical variable: $<2500$ and $\geq 2500$ g. The two categories were defined by the low birth weight (LBW) limit of 2500 g (Gowen, 2006). Birth weight was also analysed after distribution into five categories. The lowest category is based on the LBW limit and the others were based on quartile limits.

Norway is geographically spread from 58 to 72° latitude north and the variation in UV radiation is large. The variable 'place of birth', with the categories 'North Norway' and 'South Norway', was created using the separation line located approximately at 62° latitude north.

The variables 'mother's age' and 'father's age' were polytomised into quartiles, and the 75% quartile limits were used to create two levels in each variable: younger and older parents. We have missing data on father's age (cases, $n = 32$ and controls, $n = 8305$).

**Statistical analysis**

We have used an explanatory aetiological strategy, where the association of the exposition (birth weight) and the disease (melanoma) was the major focus (Abdelnoor and Sandven, 2006). The crude associations between the exposition birth weight and the disease melanoma and between the covariates and the outcome were estimated by the odds ratios (ORs) and the 95% confidence interval limit (95% CI) (contingency tables). To calculate the effect of the continuous variables, the Student’s $t$-test was used. The gradient effect between different birth weight expositions and the incidence of melanoma was done using the Mantel–Haenszel test of linear trend. Stratified analysis (Mantel–Haenszel method) was used to pinpoint effect modification via the Breslow–Day test of heterogeneity. Quantification of confounding was done by comparing the crude estimate of OR and the adjusted Mantel–Haenszel OR. A logistic multivariable model was used to control for multiconfounders (Kleinbaum et al, 1982). The statistical analyses were performed using SPSS Version 14.0 for Windows (SPSS Inc., Chicago, IL, USA). For the power calculation and for the test of linear trend, Epi Info for Windows Version 3.3.2, 2005 (Centers for Disease Control and Prevention, Atlanta, GA, USA) was used.

**RESULTS**

A total of 709 histologically verified incident cases of invasive melanoma were diagnosed in the study population. The group of cases had gender distribution of 68.0% women and 32.1% men. The OR of melanoma for women was 2.35 (95% CI: 2.01–2.76) in relation to men. The risk of melanoma was 30% higher (OR = 1.30, 95% CI: 1.09–1.55) for individuals born in the south, as compared to individuals born in the north (Table 1). Evaluation of the difference in maternal or paternal age at birth using $t$-test showed no statistically significant difference between the case and the control groups. Similarly, no difference was found when parental age was assessed as a categorical variable (Table 1). Maternal pregnancy factors such as preeclampsia/eclampsia, hypertension during pregnancy and chronic kidney disease, occurred less frequently among the cases; however, the difference was not significant. Table 1 also shows that the risk of melanoma in twins tends to be lower than in singletons (OR = 0.76, 95% CI: 0.40–1.41) though not significantly, possibly due to lack of power.

**Birth weight**

The controls had a lower mean birth weight, regardless of whether the genders were combined or separated for analysis (Table 1). However, the difference was not statistically significant. Individuals with a birth weight below 2500 g tended to have a reduced risk of melanoma (OR = 0.86, 95% CI: 0.57–1.31). In this study population, the mean birth weights were 2640 and 3524 g for twins and singletons, respectively.

In the Mantel–Haenszel test of linear trend, the individuals in the highest quartile of birth weight ($\geq 3860$ g) had an OR of 1.19 (95% CI: 0.77–1.84) compared to individuals in the lowest category ($<2500$ g) (Table 2). There was no trend in risk across the distribution of birth weight.

Results from the stratified analysis, estimating the risk of melanoma associated with birth weight, independent of gender, showed the adjusted Mantel–Haenszel OR of 0.84 (95% CI: 0.55–1.27), which corresponds to a confounding effect of $-2.3\%$. The confounding effect for each of the other variables in the analysis (place of birth, mother’s and father’s ages at time of birth) was below 5%. No effect modification was observed (data not shown).

Table 3 gives the results from the multiple logistic regression analysis, estimating the effect of multiconfounders. Birth weight below 2500 g seems to reduce the risk of melanoma later in life, also when possible confounding variables such as gender, place of birth, maternal and paternal age were included in the analysis (OR = 0.81, 95% CI: 0.52–1.26). The model confirmed the results from the univariable analysis (Table 1).

A power calculation was performed for the effect of OR = 0.81, considering the frequency of exposition to birth weight $<2500$ g in controls to be 3.7% (Table 1), with a type I error of 5% and with a power of 80%. A sample size of 5864 cases of melanoma and 891328 controls would be needed to have a 80% chance to observe a significant 19% reduction in melanoma risk in individuals with birth weight below 2500 g.

**DISCUSSION**

We questioned whether individuals with a LBW were less likely to develop cutaneous malignant melanoma compared to individuals with higher birth weight.

Results from the univariable and the multivariable analyses indicate that birth weight might be associated with occurrence of melanoma, also when other possible confounders, such as gender, place of birth and parental age were included in the model.

In 2001, Andersson et al (2001) observed a 2-fold increase in cancer risk in the highest quintile of birth weight compared to the lowest quintile (relative risk (RR) = 2.07, 95% CI: 1.22–3.50). A study published by McCormack et al (2005) did not find any association between birth weight and the occurrence of melanoma (hazard ratio = 1.03, 95% CI: 0.85–1.26). Ahlgren et al (2007) observed a positive linear trend for birth weight and incidence of melanoma (847 melanoma cases) with RR of 1.04 (95% CI: 1.00–1.31). Our data confirm the results of the last study although with nonsignificance. The study of Andersson and co-workers included only six cases of melanoma, analysed together with other cancer types under the term ‘nonhormonal cancers’, and the results are, therefore, difficult to evaluate. McCormack’s study included 77 melanoma cases and the question of power is pertinent.

The observed tendency to reduced melanoma risk among twins agrees with the tendency to lower risk among those with birth weight below 2500 g, as the mean birth weight for twins was 2640 g. Maternal preeclampsia/eclampsia, hypertension during pregnancy and chronic kidney disease may influence the nutrition conditions
in the womb and often lead to undernutrition of the foetus. These conditions were more frequent among controls than in the case group. These observations might support our hypothesis that LBW can reduce the risk of melanoma later in life.

In the present study, women have close to 2.5-fold risk of developing melanoma compared to men. This is possibly due to the different sun exposure habits between genders, but other factors might also be involved. Individuals born in the south of Norway had a 30% higher risk of melanoma compared to individuals born in the north. This result is due to the latitude gradients in UV exposure in Norway, which previously has been shown to be reflected in the melanoma risk (Magnus, 1973; Robsahm and Tretli, 2001; Cancer in Norway, 2006). No effect was

Table 1 Distribution of major variables in cases of malignant melanoma of the skin and controls without malignant disease

| Variables                          | Cases (N = 709) | Controls (N = 108 209) | OR (95% CI) | P-value* |
|------------------------------------|-----------------|------------------------|-------------|----------|
| **Birth weight (grams)**           |                 |                        |             |          |
| Mean (s.d.)                        | 3510.4 (540.9)  | 3507.8 (550.2)         | 0.900       |          |
| Females: mean (s.d.)               | 3475.9 (533.4)  | 3441.3 (531.7)         | 0.154       |          |
| Males: mean (s.d.)                 | 3583.6 (550.7)  | 3567.8 (559.8)         | 0.671       |          |
| **Birth weight (grams)**           |                 |                        |             |          |
| <2500 (%)                          | 23 (3.2)        | 4043 (3.7)             | 0.86 (0.57–1.31) | 0.491    |
| ≥2500 (%)                          | 686 (96.8)      | 101466 (96.3)          | 1.00        |          |
| **Gender**                         |                 |                        |             |          |
| Females (%)                        | 482 (68.0)      | 51 326 (47.4)          | 2.35 (2.01–2.76) | <0.0001  |
| Males (%)                          | 227 (32.0)      | 56 883 (52.6)          | 1.00        |          |
| **Place of birth**                 |                 |                        |             |          |
| South Norway (%)                   | 546 (77.0)      | 78 007 (72.1)          | 1.30 (1.09–1.55) | 0.004    |
| North Norway (%)                   | 163 (23.0)      | 30 202 (27.9)          | 1.00        |          |
| **Mother’s age (years)**           |                 |                        |             |          |
| Mean (s.d.)                        | 26.0 (5.1)      | 26.0 (5.2)             | 0.831       |          |
| <29 (%)                            | 524 (73.9)      | 76 970 (71.1)          | 0.87 (0.74–1.03) | 0.104    |
| ≥29 (%)                            | 185 (26.1)      | 31 239 (28.9)          | 1.00        |          |
| **Father’s age (years)**           |                 |                        |             |          |
| Mean (s.d.)                        | 29.7 (6.2)      | 29.7 (6.1)             | 0.844       |          |
| <33 (%)                            | 492 (72.7)      | 72 978 (73.0)          | 1.02 (0.86–1.21) | 0.827    |
| ≥33 (%)                            | 185 (27.3)      | 26 926 (27.0)          | 1.00        |          |
| **Maternal pregnancy factors**    |                 |                        |             |          |
| Preeclampsia/eclampsia (%)         | 18 (2.5)        | 3799 (3.5)             | 0.72 (0.43–1.17) | 1.161    |
| Hypertension during pregnancy (%)  | 8 (1.1)         | 1487 (1.4)             | 0.82 (0.38–1.70) | 0.575    |
| Chronic kidney disease (%)         | 2 (0.3)         | 962 (0.9)              | 0.32 (0.05–1.28) | 0.085    |
| Anaemia (%)                        | 4 (0.6)         | 586 (0.5)              | 1.04 (0.33–2.89) | 0.796    |
| **Twin status**                    |                 |                        |             |          |
| Twins+ (%)                         | 10 (1.4)        | 2009 (1.9)             | 0.76 (0.40–1.41) | 0.380    |
| Singletons (%)                     | 699 (98.6)      | 1062 200 (98.1)        | 1.00        |          |

CI = confidence interval; OR = odds ratio (crude); s.d. = standard deviation; twins+ = twins, triplets, quadruplets and quintuplets. *All P-values are two sided. *Missing data n = 8337 individuals.

Table 2 Association between different levels of birth weight and occurrence of melanoma in the study population: Mantel–Haenszel test of linear trend

| Birth weight (grams) categories | Cases (N = 709) | Controls (N = 108 209) | OR 95% CI | P for trend |
|---------------------------------|-----------------|------------------------|-----------|------------|
| <2500                           | 23              | 4043                   | 1.00      | 0.871      |
| 2500–3189                       | 160             | 22 909                 | 1.23 (0.79–1.90) |          |
| 3190–3519                       | 176             | 26 664                 | 1.16 (0.75–1.79) |          |
| 3520–3859                       | 167             | 27 506                 | 1.07 (0.69–1.65) |          |
| ≥3860                           | 183             | 27 087                 | 1.19 (0.77–1.84) |          |

CI = confidence interval; OR = odds ratio. *P for trend = 0.871

Table 3 Birth weight and risk for malignant melanoma: adjustment for multiconfounding effect of gender, place of birth and parental age at the time of birth, using multivariate logistic model

| Variable                          | OR   | 95% CI | P-value* |
|-----------------------------------|------|--------|----------|
| **Birth weight (grams)**          |      |        |          |
| <2500                             | 0.81 | 0.52–1.26 | 0.352    |
| ≥2500                             | 1.0  |        |          |
| **Gender**                        |      |        |          |
| Female                            | 2.38 | 2.02–2.80 | <0.001   |
| Male                              | 1.0  |        |          |
| **Place of birth**                |      |        |          |
| South Norway                      | 1.27 | 1.06–1.53 | 0.010    |
| North Norway                      | 1.0  |        |          |
| **Mother’s age**                  |      |        |          |
| Continuous                        | 0.99 | 0.96–1.01 | 0.236    |
| **Father’s age**                  |      |        |          |
| Continuous                        | 1.01 | 0.99–1.03 | 0.382    |

CI = confidence interval; OR = odds ratio. *All P-values are two sided.
found for parental age on risk of melanoma, which agrees with the results published by Janerich et al (1989).

Results from the present study indicate that LBW (<2500 g) might be associated with lower risk of melanoma later in life. Birth weight is probably not a risk factor of melanoma, but it might be a marker of other relevant factors. Investigation of other exposures correlated with birth weight should therefore be investigated in the future.

REFERENCES

Abdelnoor M, Sandven I (2006) Etiologisk versus prognostisk strategi i klinisk epidemiologisk forskning. Norsk Epidemiologi 16: 77 – 80

Ahlgren M, Wohlfahrt J, Olsen LW, Sørensen TI, Melbye M (2007) Birth weight and risk of cancer. Cancer 110: 412 – 419

Alexander GR, Kogan M, Martin J, Papiernik E (1998) What are the fetal growth patterns of singletons, twins, and triplets in the United States? Clin Obstet Gynecol 41: 114 – 125

Andersson SW, Bengtsson C, Hallberg L, Lapidus L, Niklasson A, Wallgren A, Hultén L (2001) Cancer risk in Swedish women: the relation to size at birth. Br J Cancer 84: 1193 – 1198

Cancer Registry of Norway (2006) Cancer in Norway 2005. Cancer incidence, mortality, survival and prevalence in Norway. Oslo: Cancer Registry of Norway

Franco-Lie I, Iversen T, Tretli S, Kringlen E, Berg K, Abdelnoor M (2005) Malignant melanoma of the skin: risk, tumour characteristics and mortality in adult twins born in Norway between 1905 and 1945 – a cohort study. Melanoma Res 15: 461 – 466

Gowen Jr CW (2006) Assessment of the mother, fetus, and newborn. In: Nelson Essentials of Pediatrics. Kliegman RM, Jenson HB, Marcdante KJ, Behrman RE (eds), 5th edn, pp 271 – 297. Philadelphia: Elsevier Inc.

Hemminki K, Chen B (2005) Are twins at risk of cancer: results from the Swedish family-cancer database. Twin Res Hum Genet 8: 509 – 514

Hemminki K, Li X (2002) Cancer risks in twins: results from the Swedish family-cancer database. Int J Cancer 99: 873 – 878

Hjalgrim LL, Rostgaard K, Hjalgrim H, Westergaard T, Thomassen H, Hemminki K, Li X (2002) Cancer risks in twins: results from the Swedish family-cancer database. Int J Cancer 99: 873 – 878

Irgens LM (2000) The Medical Birth Registry of Norway. Epidemiological research and surveillance throughout 30 years. Acta Obstet Gynecol Scand 79: 435 – 439

Iversen T, Tretli S, Kringlen E (2001) An epidemiological study of cancer in adult twins born in Norway 1905 – 1945. Br J Cancer 84: 1463 – 1465

Janerich DT, Hayden CL, Thompson WD, Selenskas SL, Mettlin C (1989) Epidemiologic evidence of perinatal influence in the etiology of adult cancers. J Clin Epidemiol 42: 151 – 157

Kleinbaum DG, Kupper LL, Morgenstern H (1982) Epidemiologic Research: Principles and Quantitative Methods. New York: Van Nostrand Reinhold Company Inc.

Le Marchand L, Kolonel LN, Myers BC, Mi M-P (1988) Birth characteristics of premenopausal women with breast cancer. Br J Cancer 57: 437 – 439

Magnus K (1973) Incidence of malignant melanoma of the skin in Norway, 1955 – 1970. Variations in time and space and solar radiation. Cancer 32: 1275 – 1286

McCormack VA, dos Santos Silva I, Koupil I, Leon DA, Lithell HO (2005) Birth characteristics and adult cancer incidence: Swedish cohort of over 11,000 men and women. Int J Cancer 115: 611 – 617

Michos A, Xue F, Michels KB (2007) Birth weight and risk of testicular cancer: a meta-analysis. Int J Cancer 121: 1123 – 1131

Neale RE, Mineau G, Whiteman DC, Brownhill PA, Murphy MF (2005) Childhood and adult cancer in twins: evidence from the Utah genealogy. Cancer Epidemiol Biomarkers Prev 14: 1236 – 1240

Nilsen TI, Romundstad PR, Troiis R, Vatten LJ (2005) Birth size and subsequent risk for prostate cancer: a prospective population-based study in Norway. Int J Cancer 113: 1002 – 1004

Robsahm TE, Tretli S (2001) Cutaneous malignant melanoma in Norway: variation by region of residence before and after the age 17. Cancer Causes Control 12: 569 – 576

Roman E, Ansell P, Bull D (1997) Leukaemia and non-Hodgkin’s lymphoma in children and young adults: are prenatal and neonatal factors important determinants of disease? Br J Cancer 76: 406 – 415

Tibblin G, Eriksson M, Cnattingius S, Ekbohm A (1995) High birth weight as a predictor of prostate cancer risk. Epidemiology 6: 423 – 424

Vatten LJ, Mahle BO, Lund Nilsen TI, Tretli S, Hsieh CC, Trichopoulos D, Stuver SO (2002) Birth weight as a predictor of breast cancer: a case-control study in Norway. Br J Cancer 86: 89 – 91

Wanderås EH, Grotmol T, Fosså SD, Tretli S (1998) Maternal health factors important determinants of disease? Br J Cancer 76: 406 – 415

ACKNOWLEDGEMENTS

We acknowledge the services of the Medical Birth Registry of Norway for supplying of birth record data used in the study. This work did not receive any funding.

Conflict of interest

The authors declare no competing interests.