

ORIGINAL ARTICLE

Previous pregnancy is a favourable prognostic factor in women with localised cutaneous melanoma

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Abstract

Background. The influence of pregnancy on survival in melanoma has been a controversial issue. **Objective.** In this retrospective study we investigated whether pregnancy (overall or temporally melanoma-related) has any effect on melanoma progression or patient outcome. **Methods.** Patient data were collected from Turku University Hospital records concerning all women in fertile age (15–45 years) and diagnosed with melanoma between January 1, 1990 and December 31, 2009. We collected data on melanoma characteristics, treatment, pregnancies and patient outcomes. **Results.** Of the 334 patients, 248 (74%) had been pregnant in some point during their life while 55 (17%) were nulliparous. The history of pregnancies could not be verified in 31 women (9%). Progression of melanoma to advanced stage was found in 58 (17%) of these women. Altogether, 35 women (14%) with at least one pregnancy had disease progression in contrast to 14 women (26%) with no pregnancies ($p = 0.049$). Women with at least one pregnancy had a 94% probability to survive from melanoma compared to nulliparous women of whom only 83% survived ($p = 0.041$). In Multivariate (COX) analysis pregnancy was a favourable factor for disease-specific survival (DSS) (HR 3.75; 95% CI 1.24–11.34; $p = 0.019$) when adjusted for age (HR 1.064; 95% CI 1.00–1.13; $p = 0.50$), localisation and stage ($p = 0.040$), and Breslow (HR 1.32; 95% CI 1.10–1.58; $p = 0.002$). However, when ulceration of the primary tumour was included in the multivariate model, Breslow remained as the only independent predictor of DSS (HR 1.58; 95% CI 1.34–1.86; $p = 0.0001$) and pregnancy was dropped from the stepwise backward model in the step preceding the last one ($p = 0.081$). **Conclusion.** Pregnancy is not a risk factor for disease recurrence or progression in melanoma patients, but instead can exert some favourable influence on prognosis.

Cutaneous melanoma is one of the most frequently diagnosed malignancies during pregnancy, besides breast cancer and cervical cancer [1]. Usually, 35% of melanoma patients are in gestational age (between 15 and 44 years) at time of diagnosis [2]. For many years there have been concerns that hormonal and immunological changes during pregnancy may be important in the development and progression of melanoma. Several pro-angiogenic growth factors such as hepatocytic growth factor (HGF), vascular endothelial growth factors (VEGFs), and placental growth factor (PIGF) are released during pregnancy and at least the latter two growth factors are known to be expressed in melanomas and dysplastic nevi [3].

The influence of pregnancy on survival in melanoma has long been a controversial issue. Previous

studies have found pregnancy as a risk factor for melanoma progression [4] whereas some others suggest that there is no difference in survival among pregnant/non-pregnant women [5]. Lens and Bataille [6] showed in their meta-analysis that exogenous or endogenous female hormones do not contribute significantly to increased risk of melanoma. Similarly, menopausal hormone therapy does not increase melanoma risk [7].

Since 1990s, several case-control and population-based studies have suggested that there is no correlation with pregnancy and poorer prognosis of melanoma [8]. Instead, O'Meara et al. [8] reported that the outcome for a woman with localised melanoma associated with pregnancy is excellent. However, in another study, the risk for cause specific death was increased if melanoma was diagnosed

during pregnancy [1]. Interestingly, melanoma is also one of the cancers in which fertility is usually preserved at similar level than in healthy age-matched controls, even though disease is treated in adolescence [9].

Melanoma is the most common malignancy to metastasise to placenta and fetus [10] but these metastases are rare [11]. Estimated incidence of secondary fetal melanoma after stage IV maternal disease is 6.4% [12]. In a French study with 22 women, the authors did not find any dismal effect of pregnancy on the outcome of metastatic melanoma patients [12].

The primary object of this study was to evaluate whether overall survival is different in women with pregnancy (in general) and in those with pregnancy temporally related to their melanoma diagnosis. In particular, we wanted to know if pregnancy within three years before or after melanoma diagnosis has any effect on melanoma progression and overall prognosis of these women. We also gathered detailed information on pregnancy, delivery, and infant health to find out whether melanoma had any impact on outcome or infants.

Materials and methods

Patients

This is a population-based, retrospective cohort study of all patients diagnosed with malignant cutaneous melanoma at Turku University Hospital between January 1, 1990 and December 31, 2009. Except for the time period, eligibility criteria for inclusion in the study required that subjects be women, who were in reproductive age (between 15 and 45 years) during this time period, and diagnosed with local or advanced cutaneous melanoma. Data on melanoma characteristics, treatment, pregnancies and outcomes of mother and child were collected from the hospital records. Altogether 334 cases were found. During the melanoma diagnosis, the median age of these women was 45.9 years (range 15.5–64.4 years). Patient characteristics are shown in (Table I). Of interest was the timing of pregnancy related to melanoma diagnosis, and women with their pregnancy within three years (before or after) from diagnosis were analysed as a separate group, defined <3> as year-group.

We also recorded the history on other chronic diseases and other malignant tumours in this cohort: 8/334 (2.4%) had history of rheumatoid arthritis, 13/334 (3.9%) had diabetes, 16/334 (4.8%) had asthma, 17/334 (5.1%) had hypothyroidism, while 46/334 (13.8%) had a high blood pressure under continuous medication. In addition, 37 (11.1%)

women had also other malignancy, usually in situ cancer or invasive breast cancer (n = 14).

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Statistical analysis

Statistical analyses were done using two statistical software packages: IBM SPSS 18.03 for Windows (IBM, NY, USA) and STATA/SE 11.2 software (STATA Corp., Texas, USA). Frequency tables were analysed using the χ^2 test, with likelihood ratio (LR) or Fischer's exact test being used to assess the significance of the correlation between the categorical variables. Odds Ratios and their 95% Confidence Intervals (CI) were calculated where appropriate, using the exact method. Differences in the means of continuous variables were analysed using non-parametric tests (Mann-Whitney or Kruskal-Wallis) for 2- and multiple independent samples, respectively. Analysis of variance (ANOVA) was only used for deriving the mean values (and their 95%CI) of each individual stratum. Univariate survival analysis for the outcome measure (DSS, progression-free survival; PFS) was based on Kaplan-Meier method, with log-rank (Mantel-Cox) comparison test. To assess the value of <3>-year pregnancy as an independent predictor, multivariate survival analysis was performed, using the Cox proportional hazards regression model (stepwise backward approach) controlling for the confounding by the following variables: age, localisation, Breslow thickness, stage, and ulceration. In all tests, the values $p < 0.05$ were regarded statistically significant.

Missing values were excluded analysis by analysis, not using the listwise exclusion option (e.g. in ANOVA). Missing values were explored using the SPSS software's missing value analysis option. No definite pattern was established for missing values, which seemed to be missing completely at random, e.g. the data on tumour ulceration in 30% of patients. Thus, it was decided to base all analysis on the existing data only, even if aware that ulceration is an important prognostic factor.

Results

Patient characteristics

Altogether, 334 women diagnosed with cutaneous melanoma and at gestational age between January 1, 1990 and December 31, 2009 were included in the study. Two hundred and forty-eight women had been pregnant at least once in their lifetime (+ group) and 55 had never been pregnant (– group). The history

Table I. Patient characteristics of all patients (n = 334) at the time of diagnosis of primary melanoma. Analysis for tumour ulceration has been routinely used only since 2005. Sentinel node biopsy (SNB) has been routinely performed since October 2001 and only in cases of Breslow ≥ 0.5 –1.0 mm melanomas.

Characteristic	Patients with pregnancy 248	No pregnancies 55	Not known 31
Age at dg, years mean (range)	45.6 (18.7–64.4)	38.3 (15.5–63.4)	47.4 (24–63.5)
Breslow (mm) (range)	1.218 (0.1–12)	1.398 (0.2–7.6)	1.179 (0.3–6)
Clark's level			
I	3 (1.2%)	1 (1.8%)	0
II	88 (35.5%)	21 (38.2%)	5 (16.1%)
III	102 (41.1%)	20 (36.4%)	12 (38.7%)
IV	43 (17.3%)	6 (10.9%)	10 (32.3%)
V	4 (1.6%)	1 (1.8%)	1 (3.2%)
Unknown	8 (3.2%)	6 (10.9%)	3 (9.7%)
Ulceration			
Ulcerated	34 (13.7%)	11 (20%)	4 (12.9%)
Ulceration absent	136 (54.8%)	24 (43.6%)	15 (48.4%)
Ulceration unknown	78 (31.5%)	20 (36.3%)	12 (38.7%)
Primary tumour site			
Head	16 (6.5%)	3 (5.4%)	2 (6.5%)
Trunk	84 (33.9%)	17 (30.1%)	11 (35.5%)
Upper extremity	53 (21.4%)	13 (23.6%)	7 (22.6%)
Lower extremity	95 (38.3%)	21 (38.2%)	11 (35.5%)
Unknown primary	0	1 (1.8%)	0
Sentinel node biopsy (SNB)			
Negative	106 (42.7%)	19 (34.5%)	14 (45.2%)
Positive	14 (5.6%)	6 (10.9%)	4 (12.9%)
Not performed (n = 174)	128 (51.6%)	30 (54.5%)	3 (9.7%)
Tumour stage (n = 334)			
I-II (n = 306)	233 (94.0%)	46 (83.7%)	27 (87.1%)
III (n = 25)	15 (6.0%)	7 (12.7%)	3 (9.7%)
IV (n = 3)	0	2 (3.6%)	1 (3.2%)
Parity status			
1	50 ^a (20.2%)		
2	94 (37.9%)		
3	66 (26.6%)		
4	28 (11.3%)		
5	5 (2%)		
6	4 (1.6%)		
7	0		
8	1 (0.4%)		

^aAnalysis includes three patients who had at least one pregnancy but the exact amount of pregnancies could not be verified.

of pregnancies could not be accurately verified in 31 women. Overall, these women reported 602 pregnancies, including abortions and miscarriages. Total 92 women reported at least one miscarriage or abortion before their melanoma diagnosis.

Breslow thickness of the tumour was recorded for 304 women, with the mean of 1.24 mm (range 0.1–12 mm) and median 0.825 mm in the whole cohort. Mean thickness in + group was 1.22 mm (range 0.1–12 mm) and in – group 1.39 mm (range 0.2–7.6 mm; $p = 0.708$). Clark level was recorded for 317 women: I-II for 118 women and III-V for 199 women. Sentinel node biopsy (SNB) was routine procedure from October, 2001 onwards and it was performed for 163 patients (48.8%); 24 (14.7%) of them had positive sentinel nodes. Of the 334 patients

306 were of Stage I-II [T1a-T4bN0M0]; tumour ≤ 1.0 mm– > 4 mm in thickness, with or without ulceration [T1a-T4b], no regional lymph node metastasis [N0], no distal metastasis [M0], 25 were of stage III [TanyN1-N3M0]; tumour any thickness, with or without ulceration, and clinically occult or apparent lymph node metastasis [N1-N3] and only three of stage IV [TanyNanyM1]; tumour any thickness, lymph node metastasis present or absent and distant metastasis [M1] at diagnosis of the primary disease. Patient characteristics at the time of melanoma diagnosis are shown in the (Table I).

One patient had adjuvant interferon- $\alpha 2b$ therapy and two had radiation therapy. Altogether 27 patients received chemotherapy or chemoimmunotherapy for their metastatic disease.

The mean follow-up time was 53.2 months (median 32 months) (range 0.2–414 months) in the whole cohort. It was 52.9 months in + group and 62.6 months in – group. At the end of the follow-up, 33 patients (9.8%) were dead, of whom 28 (8.3%) due to their melanoma.

Pregnancy and progression of melanoma

Mean progression free survival (PFS) time in the whole patient cohort was 46.9 months (range 0–414 months). Melanoma reoccurred or progressed to advanced stage during follow-up in 58 patients (58/334; 17.4%). In most cases, progression was detected as distant metastases (35 patients) and in 23 cases only in local lymph nodes. Altogether, 35/248 patients (14.1%) with at least one pregnancy had disease progression in contrast to 14/55 patients (25.5%) with no pregnancies ($p = 0.049$; OR = 0.481; 95% CI 0.238–0.973). In Kaplan-Meier analysis, this difference is even more significant ($p = 0.028$) (Figure 1). Pregnancy was not associated with length of PFS; 48.6 months (range 0–269 months) in + group and 54.8 months (range 0–414 months) in the – group ($p = 0.531$).

Pregnancy and survival with melanoma

Pregnancy was associated with higher probability to survive after melanoma when compared to nulliparous women: 16/248 (6.5%) of women in the + group and 9/55 (16.5%) in the – group died of melanoma ($p = 0.022$), indicating a significantly increased risk for disease-specific death with HR = 2.92 (95% CI 1.21–7.04) (Table II).

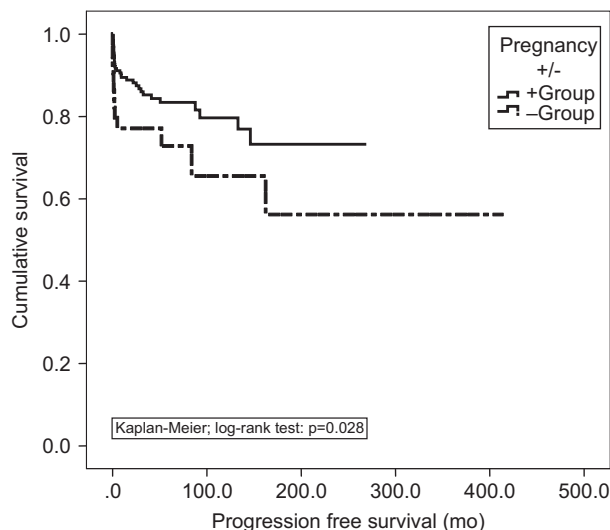


Figure 1. Probability to melanoma progression (to stage III/IV) was higher in nulliparous women (– group) than in women with history of pregnancy (+ group).

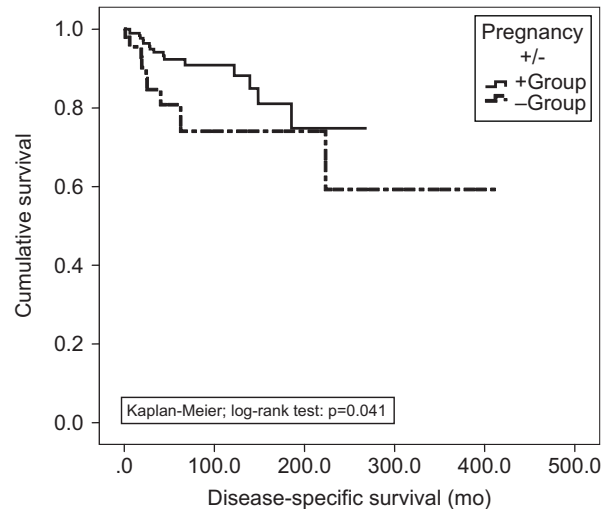


Figure 2. Disease-specific survival in women at least one pregnancy in their lifetime (+ group) compared to nulliparous women (– group).

Figure 2 shows the univariate survival (Kaplan-Meier) analysis for patients in the pregnancy + and in – groups. Patients in the former group had a 93.5% probability to survive and those in the latter had 83.0% ($p = 0.041$, Kaplan-Meier) (Figure 2). The favourable effect associated with pregnancy was found until 10 years after melanoma diagnosis (Figure 2), and the curves never crossed. Multivariate (Cox) analysis confirmed that pregnancy was an independent prognostic factor for favourable DSS when adjusted for age, Breslow, localisation and stage: age (HR = 1.064; 95% CI 1.00–1.13; $p = 0.50$), ever pregnant (HR = 3.75; 95% CI 1.24–11.34; $p = 0.019$), Breslow (HR = 1.32; 95% CI 1.10–1.58; $p = 0.002$), and stage ($p = 0.040$). However, when ulceration of the primary tumour was included in the multivariate model, Breslow remained as the only independent predictor of DSS (HR 1.58; 95% CI 1.34–1.86; $p = 0.0001$) and pregnancy was dropped from the stepwise backward model in the step preceding the last one ($p = 0.081$). The number of pregnancies was not a significant predictor in this model, and confounded (expelled) the age as independent predictor.

Mean OS for stage IV patients was 20.8 months (median 20.8, range 1.2–40.4 months).

To see if pregnancy might increase the risk for rapid progression of melanoma we separately analysed a subgroup of patients with pregnancy temporally (within three years) related to melanoma diagnosis. Altogether, 35 such women were found, of whom 25 had been pregnant during three years before melanoma diagnosis, three were pregnant during melanoma diagnosis and seven had pregnancy after < 3 years since the diagnosis. The mean age of

Table II. Outcome of study patients with or without pregnancy.

Outcome	All patients n = 303	Patients with pregnancy n = 248	No pregnancies n = 55	
Disease progression	49	35	14	p = 0.049
No progression	254	213	41	
Alive	273	229	44	p = 0.022
Death	25	16	9	
Lost to follow-up	5	3	2	

the women during their last pregnancy near melanoma diagnosis was 32.4 years (range 22.6–46.8 years). Mean Breslow thickness was 1.196 mm (range 0.3–5.0 mm). In the <3>year-group, 14 patients were Clark II, 16 were Clark III and five were Clark IV. Clark 0 or V patients were not found. In this, five patients had ulcerated melanoma and in 21 cases ulceration was absent. Ulceration was unknown in nine cases. Localisation of the primary melanoma was head in one case, trunk in 13 cases, upper extremity in seven cases and lower extremity in 14 cases. Two had positive SNB and 15 negative. SNB was not performed for 18 patients.

Mean PFS was 60 months (range 0.7–269 months) among patients in the <3>year pregnancy group. Interestingly, only 3/35 melanoma patients (8.6%) included in this group progressed during the follow-up. Melanoma-associated survival was 100% in this patient group compared with 90.5% in the other group (patients with pregnancies outside the three-year time limit and nulliparous patients) OR = 1.105 (1.065–1.146) (p = 0.046; Kaplan-Meier) (Figure 3). In multivariate survival (Cox) analysis adjusted for age, Breslow, localisation, ulceration, and stage this <3>year pregnancy was expelled from the model (no events) and the two independent predictors of DSS were Breslow: HR = 1.39 (95% CI 1.17–1.63) (p = 0.0001) and stage (p = 0.039).

We separately analysed the subgroup of 10 patients with pregnancy during or after melanoma diagnosis. In this group the mean age during diagnosis of melanoma was 29 years (range 22.6–34.2 years). In this group the mean Breslow thickness of the tumour was 1.39 mm (range 0.3–3.0 mm). Six patients were stage I, three were stage II, and one had stage III melanoma. None of these patients had any other treatment than surgery for their melanoma. The mean PFS in this subgroup was 29 months (range 0.9–82.5 months).

We also gathered all data on pregnancy outcome, premature births, infant weight and overall health. Previous melanoma diagnosis did not have any impact on these parameters, i.e. there was retardation in the intrauterine growth only in two cases. There were four deliveries before gestational age 37

weeks. Median gestational age at delivery was 39.57 weeks (range 27–42) and the mean birth weight was normal, 3525 g (range 935–5000 g). Placental or fetal metastases were not detected.

Discussion

Skin pigmentation and moles have been shown to change during pregnancy and there has been speculation whether pregnancy might promote melanoma or accelerate its growth. Lens and Bataille [6] performed a pooled analysis of 10 case-control studies including a total of 5590 women and found no association between melanoma risk and pregnancy. Multiple epidemiological studies and literature reviews suggest that pregnancy is not detrimental in a clinically localised melanoma [13]. Previous controlled trials have shown that the survival of pregnant women with melanoma is not worse than the survival of non-pregnant women with melanoma if other risk factors are ruled out [5,8,14]. Pregnancy subsequent to the diagnosis of melanoma does not worsen prognosis [5]. In our study we found that previously or subsequently diagnosed melanoma might even have favourable effect on melanoma prognosis, i.e. pregnancy seemed to be associated with reduced risk for distal metastases. Hersey and co-workers [15] have published similar findings, in which previous pregnancy was protective against death from melanoma. However, in their study other biological prognostic factors have not been determined [15]. Similarly, Lens et al. [5] have shown that pregnancy might have a modest protective effect, though not statistically significant, on melanoma prognosis.

In our study multiparity (>3 pregnancies) was associated with slightly better prognosis (95.1% vs. 90.1% alive; p = 0.117), similarly as in a previous study, in which multiparous women (>4 pregnancies) were found to have the lowest risk for new cutaneous melanomas [16].

The reasons why pregnancy might induce favourable effects on melanoma outcome can only be hypothesised. In our study one reason might be age, i.e. patients in the pregnancy + group were younger during the diagnosis of their melanoma than women

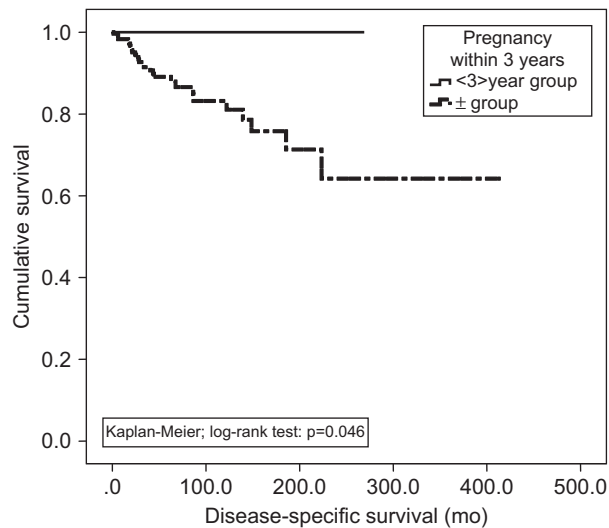


Figure 3. Disease-specific survival in women with pregnancies within three years of melanoma diagnosis (<3>year group) compared to women who had pregnancy outside this period or were nulliparous women ($\pm$ group).

with nulliparity. However, multivariate analysis of our results showed that favourable effect of pregnancy to prognosis is sustained also in age-adjusted patient populations. Our results are contrary to those of Lea et al. [17] who found that pregnancy within five years before melanoma diagnosis and multiparity are risk factors for melanoma progression in women less than 55 years of age.

Hormonal factors might be associated with better prognosis of melanoma. Increased systemic estrogen levels have been related to hyperpigmentation and nevus enlargement found during pregnancy [18]. Estrogen receptor β (ER β) is known to have tumour-suppressive effect on variety of human cancers, such as breast, ovarian, colon, and prostate cancer [19]. ER β is highly expressed in dysplastic nevi and melanoma in situ, but its expression is lost during melanoma progression [20]. De Giorgi et al. [21] found that the polymorphism of ER β gene could ascribe to a higher susceptibility to melanoma. ER receptors seem to have dual action in melanoma; ER α is proliferative and ER β anti-proliferative in melanoma cells [21]. There are no studies suggesting that increased blood estrogen levels might accelerate melanoma growth.

Obesity is a risk factor for higher incidence of melanoma among pre-menopausal women [22]. Similarly, Menzies and co-workers [23] have showed in their preliminary analysis that there is an increased risk for *B-Raf* wild-type melanoma among young obese women. We were not able to obtain any data on weight of the studied women or *B-Raf* -mutation status in their primary tumours.

Female gender itself might have favourable effect on prognosis of melanoma. Joosse and co-workers [24] have analysed over 11 000 patients with different stages of melanoma and found a consistent female advantage across all stages and different end-points. Female gender was associated with favourable outcome independently of menopausal status, tumour thickness, ulceration and number of positive lymph nodes [24].

Localisation of the primary melanoma might predict outcome. Similarly as Stensheim et al. [1] have shown in their analysis, also in our study women with pregnancies had a slightly increased proportion of head and trunk primaries when compared to their nulliparous counterparts. In our study the amount of primary melanomas in leg were 38% in both groups, pregnancy + and in pregnancy – group. Factors related to prognosis of stage I–III disease are Breslow thickness, ulceration and presence of nodal disease [25]. In earlier studies concerning pregnant melanoma patients and age-adjusted controls, pregnant melanoma patients had somewhat thicker melanomas than controls [14]. This finding was not seen in our study, in which women with previous pregnancy had thinner melanomas (mean 1.218 mm) than those who were nulliparous (mean 1.398 mm). In our study most of the women (91%) had stage I–II melanoma and only three patients were diagnosed as stage IV melanoma. The exact effect of stage (distinguish between stage IB or IIA) on prognosis in our cohort could not be determined because analysis of primary melanoma ulceration has not been a routine procedure until year 2005.

The lack of information on primary tumour ulceration and sentinel node status are the weaknesses of our study. We were able to track only 64–68% of the primary tumours in this cohort for re-analysis for tumour ulceration. In addition, sentinel node biopsy was performed only in 50% of cases, because it was only used since 2001. The proportion of ulcerated primary tumours seems to be smaller among patients with pregnancy than in nulliparous women. We included information about ulceration status to the multivariate model, and found out that Breslow thickness remained as the only independent predictor of DSS. The pregnancy was dropped from the stepwise backward model in the step preceding the last one. This finding suggests that pregnancy was the second strongest predictor for better survival in our cohort. However, due to lack of proper ulceration and sentinel node status of the whole cohort this finding is uncertain and might be changed in a more comprehensive analysis.

Most of the women studied here had been pregnant before their melanoma diagnosis. However 12 women became pregnant after melanoma diagnosis and seven of them within only three years after diagnosis. We anticipate that there is some “Healthy

mother effect" seen also in our study cohort [1]. Stensheim et al. [1] have shown that the risk of cause-specific deaths is significantly decreased for women who had postcancer pregnancies. However, in our study the amount of postcancer pregnancies was minimal (12; 4.8%) if compared to the total cohort. Thus we think that this selection bias is not enough to explain the favourable effect of pregnancy to melanoma outcome.

We also found that incidence of melanomas or their progression was not increased after pregnancy, i.e. pregnancy seems not to promote formation of melanoma micrometastases in spite of large growth factor burden in pregnancy.

We conclude that pregnancy has not negative effect on the prognosis of malignant melanoma. Women at gestational age can be advised that pregnancy does not worsen outcome of localised cutaneous melanoma.

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