The impact of comorbidity and stage on prognosis of Danish melanoma patients, 1987–2009: a registry-based cohort study

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Background: Comorbid conditions may play an important role in the prognosis of melanoma patients but have received little attention.

Methods: Using data from Danish registries, we identified patients diagnosed with melanoma from 1987 to 2009. We estimated the prevalence of comorbidity and calculated mortality rate ratios and interaction risks between melanoma and comorbidity. For every melanoma patient, 10 individuals were selected for comparison. Individuals in the comparison cohort were matched to their corresponding melanoma patients on age, gender, and exact prevalent comorbidities.

Results: We included 23 476 patients, 81% of whom had no comorbidity. Higher prevalence of comorbidity was associated with more advanced cancer stage. The standardised mortality rate increased with increasing level of comorbidity in both cohorts and was consistently higher among melanoma patients. Melanoma and comorbidity interacted to increase the mortality rate. The highest proportional excess was seen in melanoma patients with comorbidity score 3, in whom interaction accounted for 77 deaths per 1000 person-years (40% of the total rate). We stratified by cancer stage and found that the interaction was markedly concentrated in patients with distant metastases.

Conclusion: Interaction between melanoma and comorbidity was primarily concentrated in patients with distant metastases, which raises the possibility that comorbidity is associated with delay of melanoma diagnosis, advanced cancer stage, and less aggressive melanoma treatment.

The incidence of cutaneous melanoma has been rising in fair-skinned populations throughout the world (Diepgen and Mahler, 2002; Lens and Dawes, 2004; Lasithiotakis et al, 2010); the highest rates in Europe are in the North (de Vries and Coebergh, 2004). Melanoma accounts for 4% of cancers in the Nordic countries and ∼2% of cancer deaths (Tryggvadottir et al, 2010). In 2010, 1789 Danes were diagnosed with melanoma, making it the fourth most common cancer in women and eighth most common in men (The Danish Cancer Registry, 2010).

Median age at diagnosis varies between 55 and 61 years in European and US studies (Garbe and Leiter, 2009; SEER, 2012) and has the highest age-specific incidence in people older than 65 years

(Garbe and Leiter, 2009). The elderly have more chronic diseases, and use more drugs, than younger individuals (Louwman et al, 2005; Extermann, 2007; Wedding et al, 2007; Jorgensen et al, 2012). Their comorbidities may influence cancer detection, treatment, progression, and thereby prognosis. The intensity of medical treatments for melanoma patients with metastatic disease requires careful consideration of risks and benefits, particularly if another serious illness coexists. In melanoma patients who receive treatment for metastatic disease, comorbid diseases may increase the risk of complications and worsen the existing comorbid

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Table 1. Characteristics of a cohort of patients with a diagnosis of melanoma and a comparison cohort without melanoma sampled from the general Danish population				
Characteristics	Melanoma cohort, *N*	%	Comparison cohort, *N*	%
All	23 476	100	233 021	100
Gender				
Female	13 198	56	131 216	56
Male	10 278	44	101 805	44
Age group (years)				
0–55	11 006	47	109 797	47
56–75	8897	38	88 461	38
76+	3573	15	34 763	15
Cancer stage				
Localised	19 350	82		
Regional	1442	6.1		
Distant	747	3.2		
Unknown/missing	1937	8.3		
Cancer localisation				
Limbs	9784	42		
Truncus	9096	39		
Head and neck	2794	12		
Other/unspecified	1802	7.7		
Comorbidities in the CCI				
Myocardial infarction	407	1.7	3763	1.6
Congestive heart failure	391	1.7	3366	1.4
Peripheral vascular disease	329	1.4	2961	1.3
Cerebrovascular disease	793	3.4	7469	3.2
Dementia	99	0.4	910	0.4
Chronic pulmonary disease	558	2.4	5344	2.3
Connective tissue disease	327	1.4	2970	1.3
Ulcer disease	341	1.5	3155	1.4
Mild liver disease	69	0.3	587	0.3
Diabetes I and II	478	2.0	4356	1.9
Haemiplegia	27	0.1	215	0.1
Moderate to severe renal disease	142	0.6	1151	0.5
Diabetes with end-organ failure	195	0.8	1699	0.7
Any cancer without melanoma and nonmelanoma skin cancer	915	3.9	8710	3.7
Leukaemia	51	0.2	370	0.2
Lymphoma	87	0.4	721	0.3
Moderate to severe liver disease	13	0.1	116	0.0
Metastatic solid cancer	149	0.6	1279	0.5
AIDS	5	0.02	50	0.02
Comorbidities not included in the CCI				
Atrial fibrillation	192	0.8	1661	0.7
Obesity	216	0.9	2079	0.9
Transplantation	11	0.0	79	0.0
Autoimmune disease + immunosuppressive treatment	204	0.9	1858	0.8
Autoimmune disease − immunosuppressive treatment	162	0.7	1537	0.7

Table 1. (Continued)				
Characteristics	Melanoma cohort, *N*	%	Comparison cohort, *N*	%
Comorbidity score divided into 5 groups				
Comorbidity = 0	19 032	81	190 320	82
Comorbidity = 1	2335	9.9	23 348	10
Comorbidity = 2	1352	5.8	13 363	5.7
Comorbidity = 3	418	1.8	3628	1.6
Comorbidity ⩾ 4	339	1.4	2362	1.0
Abbreviations: AIDS = acquired immune deficiency syndrome; CCI = Charlson Comorbidity Index.				

diseases, which may lead to lower performance status, decreased quality of life, and life-threatening conditions.

Despite the importance of considering comorbid diseases in the treatment and prognosis of melanoma, the association between melanoma and comorbidity has received little attention (Kaae *et al*, 2007; Birch-Johansen *et al*, 2008). No study has investigated the interaction between melanoma and comorbidity; that is, the excess rate of mortality that cannot be explained by the melanoma or the comorbid diseases acting alone. The effect of comorbidity has been investigated in other cancers – for instance, breast cancer. Several studies have shown that the risk of dying from breast cancer, and other causes, increases with increasing comorbidity (Louwman *et al*, 2005; Cronin-Fenton *et al*, 2007; Land *et al*, 2011). We hypothesised that comorbid diseases would be negatively associated with survival after melanoma diagnosis, that the more comorbid conditions present at time of diagnosis, the poorer the prognosis, and that comorbid diseases would interact synergistically with melanoma to reduce survival. To address these hypotheses, we studied a cohort of melanoma patients and a comparison cohort matched to them on age, gender, and exact prevalent comorbid diseases.

MATERIALS AND METHODS

Setting. We conducted this nation-wide population-based cohort study in Denmark, which has 5.3 million inhabitants (Frank, 2000). The National Health Service provides tax-supported health care to the Danish population, including access to hospital care. Initial diagnosis of melanoma is usually made in general practice or at a dermatological clinic. The final operative removal of the tumour is done in a department of plastic surgery. National data on hospital diagnoses and cancer incidences can be linked using a unique 10-digit civil registration number (CPR-number) assigned to all Danish residents (Frank, 2000). Approval of this project was obtained from the Danish Data Protection Agency (journal number 2011-41-6249).

Data collection. We included men and women diagnosed with melanoma (ICD 10:C43) between 1 January 1987 and 31 December 2009 identified in the Danish Cancer Registry (DCR). The DCR has collected information on primary cases of cancer since 1943, and its data have been shown to be 95% complete with a validity of 98% (Storm *et al*, 1997). The DCR includes information on date of diagnosis, cancer type, site, and extent of spread of the tumour at diagnosis. Before 2004, tumours were classified as local, regional, distant metastases, or unknown stage (Documentation of the Cancer Registry, 2009). From 2004, tumours were staged according to the AJCC/UICC TNM system (Balch *et al*, 2009). We used an algorithm that allowed us to categorise melanoma TNM stages into four groups: localised stage, regional stage, distant stage, and unknown/missing stage.

Population comparison cohort subjects. For each melanoma patient, 10 individuals without melanoma were matched on age (within 5-year intervals), sex, calendar time, and prevalent comorbid

disease(s). The index date was defined as the date of diagnosis for melanoma patients and as the date of the matched melanoma patient's diagnosis for members of the comparison cohort. If more than 10 people were eligible for matching, 10 were selected randomly. If fewer than 10 were eligible, all were selected. Comparison cohort members were matched to melanoma patients within 5-year birth year intervals (1890–1894, 1895–1899, …1990–1994).

Mortality data. Follow-up data on all-cause mortality and emigration for melanoma patients and population comparison cohort subjects were obtained from the Civil Registration System (CRS). The CRS contains information on vital status, date of death, and residence of all residents of Denmark, and is updated daily.

Data on comorbidity. Information on comorbid conditions was based on diagnosis codes from the Danish National Registry of Patients (DNRP). The DNRP includes data on nonpsychiatric in-patient hospital admissions since 1977 and on out-patient clinic visits since 1995. The DNRP includes data on admissions and discharges, surgical procedures performed, and up to 20 discharge diagnoses according to the International Classification of Diseases, 8th revision (ICD-8) until the end of 1993 and 10th revision thereafter (ICD-10). A recent study found the positive predictive value of the Charlson conditions in the DNRP to be consistently high (Thygesen *et al*, 2011). We used the diagnoses from in- and outpatient hospitalisations in the 10 years preceding the index date to identify prevalent comorbidities.

Definition of analytic variables

Comorbidity. We classified diagnoses of chronic diseases into 24 categories, based on a modified version of the Charlson Comorbidity Index (CCI; Table 1) (Charlson *et al*, 1987). Atrial fibrillation, obesity, transplants, and autoimmune diseases ± immunosuppressive treatment were included among the comorbid conditions, although they are not included in the original CCI (Charlson *et al*, 1987). Nonmelanoma skin cancers (NMSCs) comprised 30% of all preceding cancers among melanoma patients, but only 12% in the comparison cohort. Melanoma patients and comparison subjects were matched on any cancer (not specific cancer type). We did not want patients with preceding NMSCs matched to patients with cancer types that have worse prognosis (e.g., colon, lung, ovarian, and so on). We therefore excluded NMSCs from the category 'any cancer' in the CCI because of the unequal distribution between the compared cohorts.

Individuals in the comparison cohort were matched to their corresponding melanoma patients according to their exact prevalent comorbidities. For every melanoma patient, we characterised the history of the 24 comorbid diseases in the preceding 10 years. We then selected 10 comparison subjects of the same age, within 5-year intervals, and sex at the index date and with the same prevalent comorbid diseases. For example, a male melanoma patient diagnosed in 1994, 56 years old, with a history of myocardial infarction in the preceding 10 years was matched with

Table 2. Characteristics of age groups						
Age categories (years)	Comorbidity 0, N (%)[a]	Comorbidity 1, N (%)[a]	Comorbidity 2, N (%)[a]	Comorbidity 3, N (%)[a]	Comorbidity ⩾4, N (%)[a]	All, N (%)[b]
0–55						
Local	8693 (86%)	473 (83%)	203 (82%)	26 (74%)	26 (55%)	9421 (86%)
Regional	553 (5.5%)	41 (7.2%)	18 (7.3%)	5 (14%)	7 (15%)	624 (5.7%)
Distant	208 (2.1%)	13 (2.3%)	7 (2.8%)	4 (11%)	8 (17%)	240 (2.2%)
Unknown	654 (6.5%)	42 (7.4%)	19 (7.7%)	0 (0.0%)	6 (13%)	721 (6.6%)
56–75						
Local	5567 (82%)	861 (80%)	512 (76%)	148 (76%)	109 (61%)	7197 (81%)
Regional	440 (6.5%)	69 (6.4%)	61 (9.1%)	14 (7.1%)	19 (11%)	603 (6.8%)
Distant	220 (3.2%)	41 (3.8%)	43 (6.4%)	14 (7.1%)	26 (14%)	344 (3.9%)
Unknown	543 (8.0%)	110 (10%)	54 (8.1%)	20 (10%)	26 (14%)	753 (8.5%)
+76						
Local	1693 (79%)	502 (73%)	335 (77%)	125 (67%)	77 (69%)	2732 (76%)
Regional	131 (6.1%)	48 (7.0%)	19 (4.4%)	9 (4.8%)	8 (7.1%)	215 (6.0%)
Distant	91 (4.2%)	28 (4.1%)	18 (4.1%)	20 (11%)	6 (5.4%)	163 (4.6%)
Unknown	239 (11%)	107 (16%)	63 (14%)	33 (18%)	21 (19%)	463 (13%)

[a]Percentage calculated according to the number of people in specific age and comorbidity category.
[b]Percentage calculated according to the number of patients in specific age category but all comorbidity categories.

10 male comparisons born between 1935 and 1939 and with a history of myocardial infarction in the preceding 10 years. We classified patients according to CCI score divided into five strata based on the number of comorbid diseases (comorbidity = 0, 1, 2, 3, and ⩾4 diseases).

Follow-up. Melanoma patients and members of the comparison cohort were followed from the index date until first of death, censorship at emigration, or 31 December 2009.

Statistical analyses. We computed the frequency and proportion of the melanoma cohort and the comparison cohort within categories of the covariates. For information on duration of comorbidity, we calculated the median time from diagnosis of the first comorbid condition to the index date (date of melanoma diagnosis or matching) in both cohorts.

We calculated risks and rates of mortality for the melanoma cohort and the comparison cohort, stratified by comorbidity. To account for potential confounding by age and sex, we calculated mortality rates (MRs) standardised to sex and age of the comparison cohort (15–55 years, 56–75 years, and 76+ years). We computed mortality risks and rates for melanoma patients and the comparison cohort members from index date to 1 year, and from 1 to 5 years.

Using the mortality rates of the melanoma and comparison cohorts stratified by comorbidity categories, we evaluated the interaction between melanoma diagnosis and comorbidity by computing the interaction contrast, which estimates the excess rate of mortality beyond that expected from melanoma and the comorbid conditions acting independently.

RESULTS

Study population. We identified 23 476 melanoma patients and 233 021 members of the matched comparison cohort (Table 1). The majority were women (56%) and more than half (53%) were older than 55 years. According to tumour stage, 19 350 (82%) had a localised tumour, 1442 (6.1%) had regional metastases, 747 (3.2%) had distant metastases, and 1937 (8.3%) had unknown or missing stage. Among women, the most frequent localisation was on limbs (55%), whereas among men melanomas located on the trunk were the most frequent (52%).

For some melanoma patients, it was not possible to match 10 comparison individuals who had the same comorbid conditions as the melanoma patients, which explains the over-all average of 9.9 comparison cohort members for every melanoma patient.

Prevalence of comorbidities. Measurement of comorbidity resulted in 19 032 (81%) melanoma patients with comorbidity score 0, 2335 patients (9.9%) with comorbidity score 1, and 1352 (5.8%) with comorbidity score 2. In the more severe comorbidity categories, 418 (1.8%) had comorbidity score 3 and 339 (1.4%) had comorbidity score ⩾4. Any cancer (excluding melanoma and NMSC) was the most prevalent comorbidity (Table 1), diagnosed in 915 patients (3.9%). Cerebrovascular disease was diagnosed in 793 patients (3.4%), followed by chronic pulmonary disease (558 patients, 2.4%). Median duration between first registered comorbid disease and index date equaled 4.3 years in the melanoma cohort and 4.4 years in the comparison cohort (data not shown). The mean durations and standard errors were identical. Thus, there was no difference in duration of comorbid conditions between the two cohorts.

Within each age group, the majority of melanoma patients were diagnosed with localised stage (Table 2). A higher proportion of people aged ⩾76 years were diagnosed with distant metastases compared with the youngest age group, 4.6% vs 2.2%. Increased comorbidity was related to advanced cancer stage at diagnosis. In the age category 0–55 years, 25% and 32% of people with 3 or ⩾4 comorbidities had metastatic disease (regional and distant metastases) vs 7.6% in people without comorbidity. In the 56–75 category, 14% and 25% with 3 or ⩾4 comorbidities had metastatic disease vs 9.7% for people without comorbidity. In the ⩾76 years category, 16% and 13% had metastatic disease with 3 or ⩾4

Table 3. The 0–1-year mortality, mortality rate ratios, and interaction contrasts for melanoma patients compared with individuals from the comparison cohort sampled from the general population, overall and by comorbidity score

Comorbid score	Cohort	No. of individuals	No. of deaths	No. of person-years (PY)	Standard mortality rate (/1000 PY)	Mortality rate ratio (95% confidence interval)	Interaction contrast (/1000 PY)
All	Melanoma	23 476	1325	22 800		2.55 (2.40 to 2.72)	Not applicable
	Matched	233 021	5195	230 162		1.00 (reference)	
0	Melanoma	19 032	758	18 659	46.2	3.89 (3.57 to 4.23)	0 (reference)
	Matched	190 320	2055	189 118	13.5	1.00 (reference)	
1	Melanoma	2335	210	2228	66.3	1.95 (1.68 to 2.27)	1.6 (−8.9 to 12)
	Matched	23	1124	22 769	32.0	1.00 (reference)	
2	Melanoma	1352	183	1254	115.7	1.74 (1.48 to 2.04)	22 (−0.3 to 44)
	Matched	13 363	1076	12 798	61.0	1.00 (reference)	
3	Melanoma	418	88	375	189.8	1.78 (1.41 to 2.26)	76 (0.7 to 152)
	Matched	3628	439	3401	80.7	1.00 (reference)	
⩾4	Melanoma	339	86	283	345.4	1.17 (0.92 to 1.50)	101 (−8.3 to 210)
	Matched	2362	501	2076	211.6	1.00 (reference)	

Table 4. Interaction contrasts stratified on cancer stage, 0–1 year after melanoma diagnosis

	Interaction contrast for comorbidity 1 vs 0 (1000 person-years)	Interaction contrast for comorbidity 2 vs 0 (1000 person-years)	Interaction contrast for comorbidity 3 vs 0 (1000 person-years)	Interaction contrast for comorbidity ⩾4 vs 0 (1000 person-years)
All stages	1.6 (−8.9 to 12)	22 (−0.3 to 44)	76 (0.7 to 152)	101 (−8.3 to 210)
Localised	1.3 (−6.9 to 9.6)	2.7 (−18 to 23)	1.3 (−58 to 61)	−120 (−179 to −60)
Regional	−39 (−99 to 21)	1.1 (−106 to 108)	50 (−149 to 249)	−73 (−351 to 204)
Distant	448 (−358 to 1255)	277 (−169 to 723)	792 (−1003 to 2587)	1272 (−194 to 2737)
Unknown	3.2 (−38 to 44)	71 (−34 to 176)	76 (−45 to 197)	3930 (−414 to 8274)

Standardised for gender and age groups 0–55, 56–75, and 76+ years.

comorbidities *vs* 10% for people without comorbidity. The prevalence of people with unknown cancer stage increased with age, as previously reported (Froslev *et al*, 2012).

All-cause mortality. The standardised mortality rate increased with increasing comorbidity in both cohorts and was consistently higher among melanoma patients (Table 3). The standardised mortality rate for melanoma patients with comorbid score 1 was 66 per 1000 person-years during the first year after diagnosis compared with 32 in the comparison cohort. In the most severe comorbidity group (⩾4), the standardised mortality rate was 345 per 1000 person-years in the melanoma cohort compared with 212 in the comparison cohort. The mortality rate ratio (MRR) for the first year was 2.55 (95% CI: 2.40–2.72).

Interaction between melanoma and comorbidities. In the first year after melanoma diagnosis, there was substantial synergy between melanoma and comorbidity affecting mortality (Table 3). In the most severe comorbidity group (⩾4), the difference in mortality rates between melanoma patients and comparisons was 133.8 deaths (345.4 minus 211.6) per 1000 person-years. This difference in mortality rates can be ascribed to melanoma, as the melanoma patients and the comparisons are matched on comorbidity. In the group of people without comorbidity (0), the difference in mortality rates between melanoma patients and comparisons was 32.7 deaths (46.2 minus 13.5) per 1000 person-years. The difference in these two rate differences, 101.1 deaths (133.8 minus 32.7) per 1000 person-years, equals the interaction contrast, and represents the excess mortality in individuals with both melanoma and severe comorbidity

attributable to melanoma and the comorbidities affecting mortality synergistically. The mortality rate for patients with both melanoma and the most severe comorbidity category (⩾4) was 345.4 deaths per 1000 person-years, and hence 30% of this rate was due to the synergy.

The interaction contrast increased with increasing level of comorbidity. For patients with comorbidity score 1, there was virtually no interaction between comorbidity and melanoma; 1.6 deaths (2.4%) per 1000 person-years were caused by interaction. For patients with comorbidity level 2, the interaction between melanoma and comorbidity caused an excess mortality rate of 22 (19%) per 1000 person-years. The highest proportional excess was seen in melanoma patients with comorbidity score 3, for which interaction accounted for 76 deaths (40%) per 1000 person-years.

Among melanoma patients who survived the first year, interaction between melanoma and comorbidity was less pronounced (data not shown). For people with comorbidity score 1, interaction accounted for only 5.4 (7.2%) deaths per 1000 person-years, 2.0 (2.3%) deaths per 1000 person-years for comorbidity score 2, and 1.2 (1.1%) deaths per 1000 person-years for comorbidity score 3. In the most severe comorbidity group, interaction accounted for 40 deaths per 1000 person-years (24%).

Table 4 presents data on interaction contrasts between different levels of comorbidity stratified on cancer stage at the time of diagnosis. For all comorbidity levels, there was significant interaction between distant stage melanoma and comorbidity. Moreover, interaction increased with increasing level of comorbidity for people with distant stage melanoma.

DISCUSSION

In this nationwide population-based cohort study, we included 23 476 men and women diagnosed with melanoma, of whom 19 350 (82%) were diagnosed with localised stage and 4444 (19%) suffered from one or more comorbidities. People with a higher prevalence of comorbidities were diagnosed with a more advanced cancer stage than people without comorbidity and had a higher proportion of missing cancer stage. The proportion diagnosed with advanced stage increased with increasing age, and the level of comorbidity was strongly associated with mortality. Synergy between melanoma and comorbidity affecting mortality increased with increasing comorbidity, was most pronounced in the first year after melanoma diagnosis, and was concentrated in patients diagnosed with distant metastases. A Danish study from 2008 has also described decreasing survival with increasing comorbidity level for melanoma patients (Birch-Johansen et al, 2008), but did not evaluate the interaction. For cancers of the breast, lung, colon, ovaries, and prostate, high level of comorbidity is associated with poorer survival (West et al, 1996; Meyerhardt et al, 2003; Pavelka et al, 2006; Cronin-Fenton et al, 2007; Extermann, 2007; Lund et al, 2008; Tetsche et al, 2008b; Land et al, 2011; Patnaik et al, 2011).

The majority of melanoma patients (81%) had none of the selected comorbidities in the 10 years preceding their melanoma diagnosis. Another Danish study found that 87% of men had no comorbidity at the time of melanoma diagnosis, and for women this number was 94% (Birch-Johansen et al, 2008). The proportion of breast cancer patients (Cronin-Fenton et al, 2007; Land et al, 2011; Patnaik et al, 2011), prostate cancer patients (Lund et al, 2008), and ovarian cancer patients (Tetsche et al, 2008a) without comorbidity tends to be lower than this. As sun exposure is the main risk factor for melanoma (Leiter and Garbe, 2008), and sun exposure is associated with healthy habits such as exercise (Moehrle, 2008), it may be that melanoma patients are healthier, on average, than most other cancer patients. Younger median age at diagnosis of melanoma, compared with many other cancers, may also contribute to less comorbidity and healthier habits among melanoma patients.

In the remaining 19% of the melanoma cohort with some prevalent comorbidity, the most common comorbid diseases were another cancer, cerebrovascular disease, COPD, and diabetes. The CCI did not provide information on the patients' functional status, but the unique study design of matching on specific comorbid conditions should enhance comparability. Time from diagnosis of the first comorbid disease to index date was the same in the melanoma and matched comparison cohort. We therefore assumed that age-, sex-, and comorbidity-matched patients had similar functional status as the corresponding melanoma patient and thereby experienced the same biological mechanisms and received similar medical treatment for their comorbid conditions. To some extent, the study design controlled for confounding factors such as smoking and alcohol habits, as the patients were matched on diseases related to these lifestyle habits (e.g., COPD and liver diseases). The study was conducted in Denmark where everybody has free access to tax-supported health care. Differences in treatment because of socioeconomic status are unlikely, but differences in survival depending on socioeconomic status have been reported (Birch-Johansen et al, 2008). Residual differences between melanoma patients and comparisons undoubtedly exist, including differences in health behaviours, use of the health-care system, and awareness of disease.

During our study period, 1987–2010, the cancer staging system in the DCR changed. Since 2004, staging of melanoma has been performed according to the Tumour Node Metastasis (TNM) classification devised by the American Joint Committee on Cancer (Balch et al, 2009). Before 2004, another system was applied to describe the dissemination of the cancer disease (Documentation of the Cancer Registry, 2009). We integrated the two stage coding systems by an algorithm that categorised stage as local, regional, distant, or unknown. Integrating two stage systems may have led to some misclassification.

A consideration in interpreting the study is the unknown impact of age and comorbidity on receipt of melanoma therapy. During our study period, there was no standard adjuvant treatment for melanoma in Denmark. Since 1995, different regimens of interleukin-2 (IL-2)-based immunotherapy have been first-line treatment for patients with metastatic disease. Thus, interaction based on differential treatment is unlikely. To receive such a treatment or enter a trial, patients have to meet the conditions required for that treatment or trial, such as performance status, age range, haematology, history of comorbidities, and potentially other factors. Frequently, chronic conditions can exclude patients from such a treatment or trial and they will be offered another treatment if any treatment can be offered at all. During our study period, several trials have been conducted. As an example, a phase II study of subcutaneous histamine dihydrochloride, IL-2, and interferon-α was initiated in patients with metastatic melanoma in Denmark (Schmidt et al, 2002). Several medical conditions caused patients to be ineligible for treatment with IL-2 study enrolment, including symptomatic heart disease, acute myocardial infarction within 3 years, serious autoimmune disease and asthma, seizure disorders, treatment with corticosteroids, age >70 years, and specific haematological requirements. The strict enrolment criteria for entry into clinical trials may cause underrepresentation of elderly people and may exclude them from more aggressive treatment strategies because of the side effects of the therapy on physical frailty, comorbidity, and polypharmacy (Koppie et al, 2008). Less aggressive treatment for the melanoma among patients with comorbidity may explain some of the interaction between melanoma and comorbidity affecting the mortality rate.

Additional mechanisms behind the observed synergies are unknown. A plausible explanation may be that adding anticancer treatment may worsen an already reduced functional status for those with severe comorbid diseases, making these patients tolerate treatment less well than people without comorbidity. The people with comorbidity score ⩾4 are older – 86% are over 55 years vs 47% of those with comorbidity score 0 – and hence reduced function of the immune system in these older patients may contribute to the interaction between comorbidity and melanoma to affect mortality (Weinberger et al, 2008; Mazzola et al, 2012). Elderly patients, who more often had comorbid conditions, are also more often diagnosed with the nodular subtype of melanoma, which develops rapidly, lacks early symptoms, and is more aggressive (Norgaard et al, 2011). However, we were not able to distinguish between different histological types of melanoma in our data, and hence cannot explore this explanation. Older age is associated with thicker and more advanced tumours at diagnosis, resulting in higher mortality among elderly people (Lasithiotakis et al, 2010; Norgaard et al, 2011). A possible explanation for late diagnosis in people with comorbid conditions could be the comorbidities, or side effects of their treatment, disguising the symptoms of melanoma or lowering consciousness of melanoma by the patient or health-care provider. Having comorbidity and cancer (colorectal, melanoma, breast, prostate) has been associated with later detection of cancer (Gonzalez et al, 2001).

In this population-based study of melanoma patients, we found that the presence of severe comorbidity was associated with an advanced cancer stage and the proportion of people diagnosed with distant metastases increased with age. Mortality was higher among patients with comorbidities. Although there seemed to be interaction between comorbidity and melanoma during the first year after melanoma diagnosis, we found that interaction was primarily concentrated in the group of patients diagnosed with

distant metastases, which raises the possibility that comorbidity may be associated with delay of melanoma diagnosis, more advanced disease stage, and less aggressive melanoma treatment. Increased attention to optimising treatment of comorbid diseases in the first year may reduce the mortality rate.

ACKNOWLEDGEMENTS

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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