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Subsequent malignancies among survivors of multiple myeloma in Germany: cancer registry data-based analysis (1990-2011)

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BACKGROUND

The standard therapy of multiple myeloma (MM) mainly consists of combination of chemotherapy (alkylating), steroids, stem cell transplantation (being in use since 1960s-1990s), and new types of medications such as proteasome inhibitors and immunomodulatroy drugs (introduced after 2000s). Although new MM therapies have improved survival rates, particularly in younger patients (1), some types of these new therapies have been associated with increased incidence of subsequent primary malignancies (SPM) (2-6). Very few population-based studies (6, 7) have investigated the trend over time of SPM risk after MM diagnosis.

STUDY AIM

To provide detailed and up to date estimates of SPM risk following MM from the recently pooled cancer registry data in Germany.

METHODS

We calculated the indirectly standardized incidence ratio (SIR) and excess absolute risk (EAR) for developing SPM overall (ICD-10 C00-C97), and for solid (C00-C75) and haematologic malignancies (C81-C96) in adult patients diagnosed with first MM (n=39,074) from 1990 to 2011 in 14 German cancer registries. SIRs were compared across different groups of age, sex, latency, and calendar periods (1990-2000 vs. 2001-2011). The analysis by calendar period was pooled from 9 epidemiologic cancer registries.

RESULTS

- After a median follow-up time of 2 years, there was a small but significant increase in the risk of developing any SPM (SIR=1.11, EAR=14.7) compared with the general population of Germany. Patients with first MM also had a lower risk of SPM than patients with other types of haematologic malignancies, Table 1.
- Overall, risks did not generally vary by gender, but were slightly higher in patients first diagnosed with MM before 60 years of age (SIR=1.32), Figure 1.
- Solid and haematologic malignancies' SIRs were significantly elevated (by 7% and 65%, respectively); mainly for acute myeloid leukaemia (AML, 6-fold), HL (2.6-fold), cancers of the kidney, lip/oral cavity, melanoma, and NHL (1.5- to 1.8-fold), Figure 2.
- Risks for most SPM sites were elevated only within the first year of follow-up. For AML, the risk was significantly elevated within the first 10 years of follow-up, and was highest (15-fold) between one and five years in younger patients (<60 years), Figure 3. The analysis in relation to the calendar periods showed no statistically significant differences in the overall SIRs (and of AML) between the two time periods. However, SIRs for AML were notably decreased after 2000 in younger patients, and remained unchanged in older patients (≥60 years).

Table 1. Overall SIRs and EARs of subsequent malignancies following first MM compared to other haematologic malignancies

First cancer (ICD-10)	Patients	Observed SPM (%)	Expected SPM	SIR (95% CI)	EAR per 10,000 PYRs
HL (C81)	16826	953 (5.7%)	409.01	**2.33 (2.18-2.48)**	55.81
NHL (C82-C85)	99829	6788 (6.8%)	4523.95	**1.50 (1.46-1.54)**	56.82
MM (C90)	39074	1761 (4.5%)	1582.16	**1.11 (1.06-1.17)**	14.67
Leukaemia (C91-95)	75053	4478 (6%)	3118.63	**1.44 (1.39-1.48)**	51.17

SIR: standardized incidence ratio (Observed/Expected), PYRs: person-years at risk, EAR: excess absolute risk ([Observed-Expected]/PYRs), SPM: subsequent primary malignancies, MM: multiple myeloma, HL: Hodgkin lymphoma, NHL: non-Hodgkin lymphoma
Exclusions: Death Certificate only (DCO) cases, preceding primary malignancies, non-melanoma incidence cases were not considered in the analysis
Bold SIR indicates significant (95% confidence interval did not include the value 1, P<0.05)

Figure 2. SIRs by site of subsequent malignancies following first MM

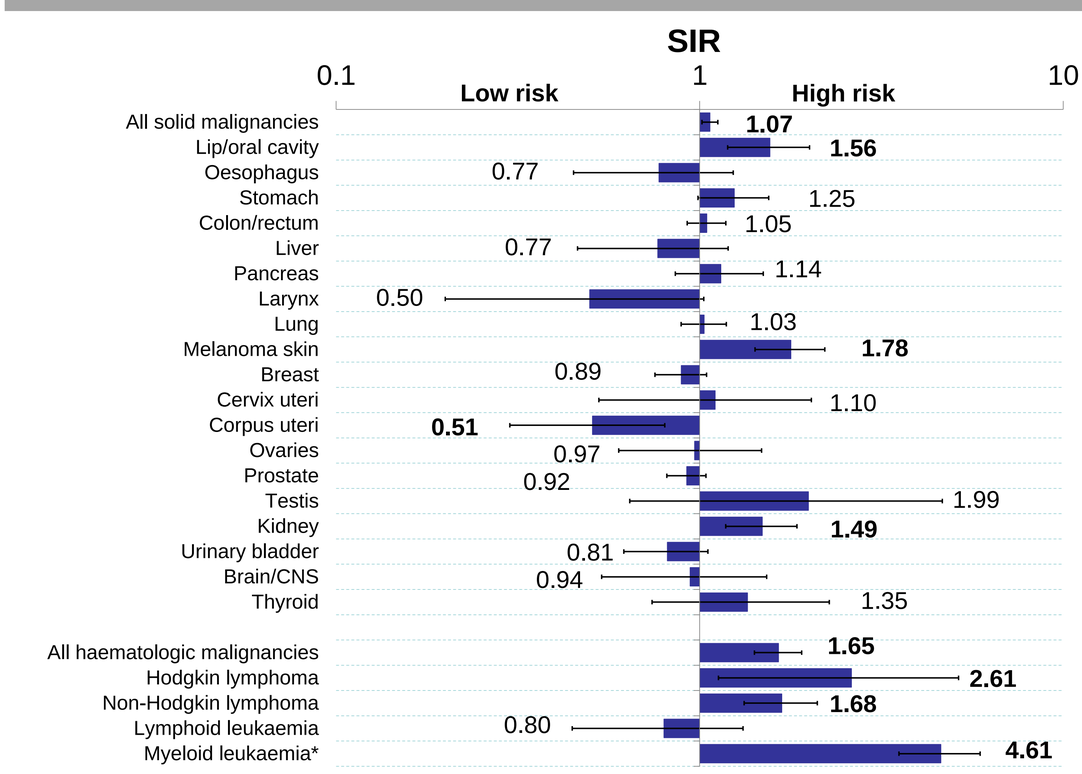


Figure 1. Overall SIRs of subsequent malignancies following first MM by age, sex, time from diagnosis and calendar periods

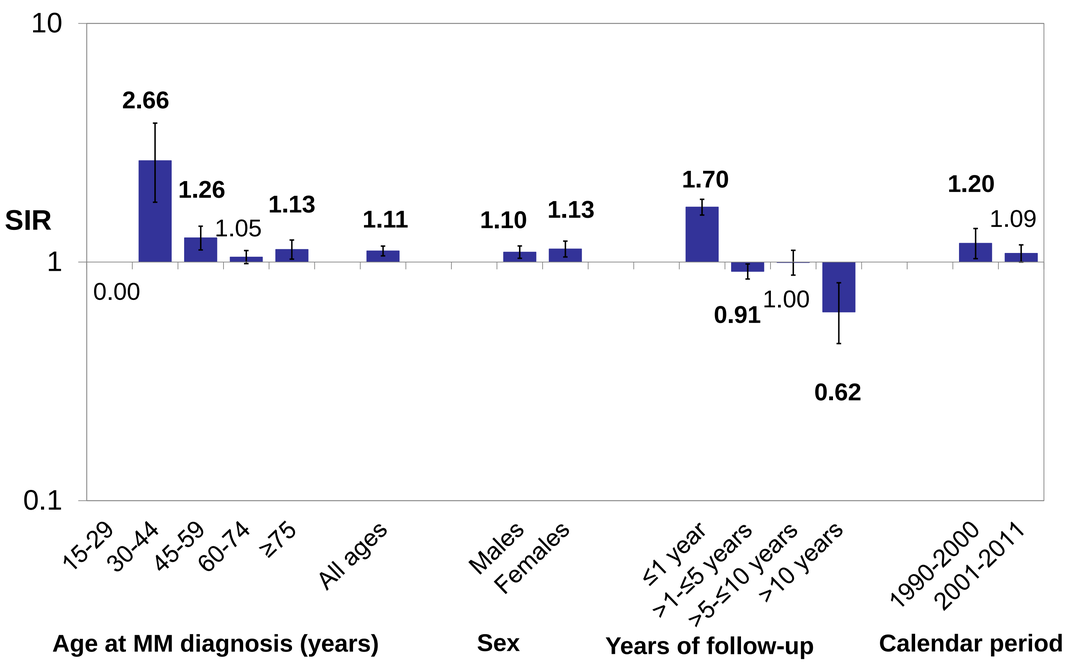
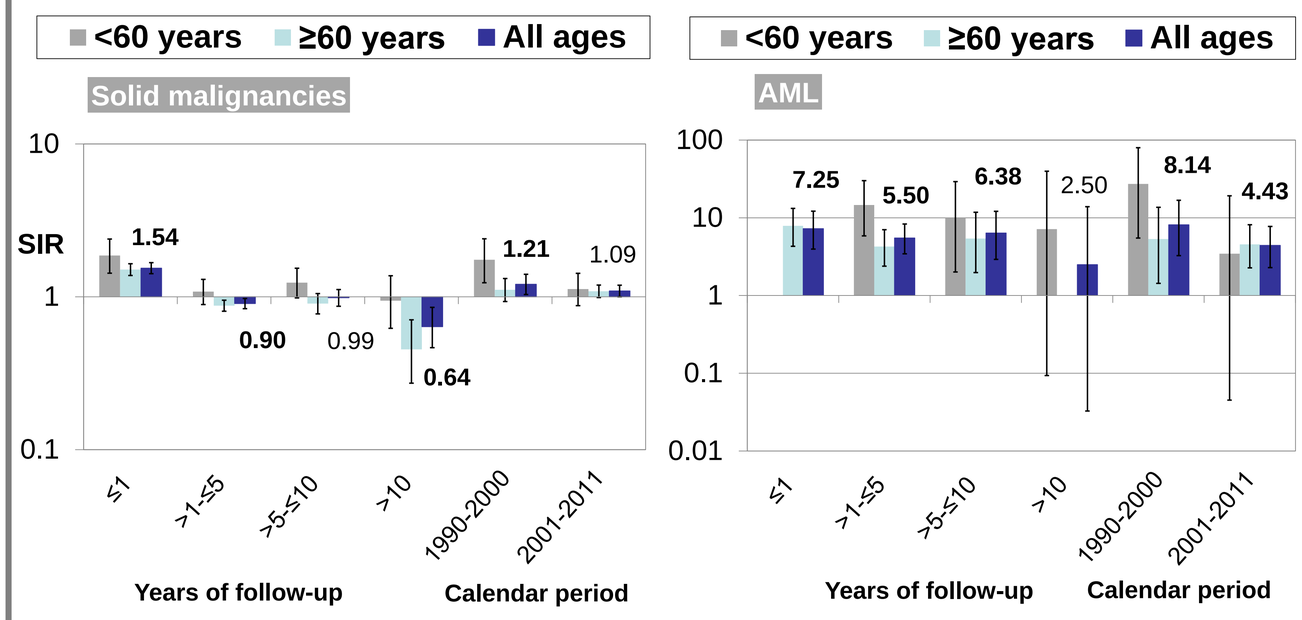


Figure 3. SIRs of subsequent solid malignancies and AML following first MM by time from diagnosis and calendar periods



DISCUSSION

German MM patients have a slight overall increased risk of SPM. As cancer registry data do not contain detailed information on treatments administered, we therefore were not able to assess their effects on SPM risk. However, we examined the relative risk in relation to time from diagnosis and calendar period, our results suggest that subsequent AML might generally be attributable to treatment. There was no trend of increase in SPM risk overall or of AML over the most recent years, similar to other population-based studies, however, the unchanged risk of AML in older patients may indicate persistent toxic effects of some MM therapies (e.g. melphalan). Our results can be considered an up-to-date estimate of SPM risk in MM survivors in Germany. Caution should be considered in interpreting the risk in relation to calendar time period as the analysis was based on very small number of observed cases and limited follow-up time. Long term monitoring of risk in MM survivors using cancer registry data should be considered to assess the impact of new therapies on SPM incidence in Germany.

Literature: (1) Sant M et al. 2014 (2) Curtis RE et al. 2006 (3) Dong C and Hemminki K. 2001 (4) Royle et al. 2011 (5) Palumbo A et al. 2014 (6) Mailankody et al. 2011 (7) Razavi P et al. 2013