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Do women with cancer have better survival as compared to men after adjusting for staging distribution?

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Background: Gender aspects in medicine are receiving increasing attention, namely also in oncology. For this reason, we decided to investigate whether for solid cancer sites women have better survival outcome than do men in the population of Tyrol, Austria. **Methods:** We conducted an observational population-based study in Tyrol. All solid cancer sites excluding non-melanoma skin cancer and sex-specific sites were analysed in total and all specific sites with more than 500 patients in the analysis. By the end of 2006, follow-up was ended. We applied a relative excess risk model, thus correcting for differences in life expectancy between women and men. **Results:** For all cancer sites combined, after adjusting for case mix, women had a relative excess risk of 0.95 (95% CI 0.91–0.99). For the following sites our analysis resulted in a relative excess risk statistically different from 1, namely for women as compared to men: head and neck without larynx 0.72 (95% CI 0.56–0.93), stomach 0.86 (95% CI 0.75–0.97) and lung 0.82 (95% CI 0.75–0.90). **Conclusion:** In a healthcare system with free access to diagnostics and therapy, after adjusting for staging distribution female cancer patients have a lesser excess mortality risk than do men for lung, stomach and head and neck cancer and also for all cancer sites combined after adjusting for case mix.

Keywords: cancer, gender, population based, prognosis, survival

Introduction

Gender aspects in healthcare systems are receiving increasing attention, but are still not adequately recognized either in terms of public health or of diagnosis and treatment. Already in the 1990s evidence for poorer survival in women was demonstrated for cardiovascular diseases.[1] On the other hand, some evidence shows better survival of female oncology patients: for some cancer sites like lung cancer better survival in women is well established, while for other cancer sites the picture is still unclear. Also, for all cancer sites combined, investigations have shown better survival for women than for men. However, the relative risk depends on age and diminishes or even reverses for older age groups.[2,3] Some authors conclude that a detailed investigation of gender aspects could lead to improvement in treatment.[4,5]

Of course, in order to establish gender as a prognostic factor, we must take into consideration that cancer is a multifactorial system. For some sites like stomach or colorectum, women are older at the time of diagnosis than are men. Furthermore, we know that in nearly all countries women have a longer life expectancy than do men.[6,7]

Properly dealing with all these factors poses methodological challenges. We know that the method of relative survival properly accounts for differences in age structure and in life expectancy.[8–10] However, these models are not so well recognized, and many publications base their analysis on Cox models.

Our main goal was to analyse survival differences between women and men for the main solid cancer sites by applying a model that adjusts for the main factors registered in a cancer registry. The analysis was performed using the incidence data set for Tyrol for years of diagnosis from 1988 (when our cancer registry was started) to 2003.

Methods

Incidence data for the population of Tyrol are collected by the Cancer Registry of Tyrol. The cancer registry was established in 1986, and data have been registered on a population basis since 1988. Also since 1988, our registry data have been published data in Cancer Incidence in Five Continents,[11–13] thus giving evidence of good completeness of the incidence data.

Assessment of patient life status is passive. We do a probabilistic record linkage between incidence data and the official mortality data set for Tyrol collected by Statistics Austria.[14,15]

We analysed all patients with solid cancer cases in the incidence data set for Tyrol with year of diagnosis from 1988 to 2003, $N = 43\,987$. DCO cases ($N = 1945$), cases found at autopsy ($N = 494$) and non-melanoma skin cancer (NMSC) cases ($N = 2969$) were excluded. In addition, for eight cases we could not identify patient status; these cases were also excluded from the analysis. Analysis was restricted to adult patients (defined as age $\geq$20 years). For patients with multiple cancer sites, only the chronologically first cancer was included in the analysis. Finally, we excluded sex-specific cancer sites. We ended up with an analysis data set of 21 102 cases. Closure of this study was end of 2006.

We analysed all sites for which we had at least 500 cases. The number of 500 derives from applying rules of thumb proposed by Harrell *et al.*[16] For an overview of all solid cancer sites, we aggregated all solid cancer sites without gender-specific sites (this means we excluded the female cancer sites ovary, cervix, corpus and other gynaecological sites and the male sites prostate, testis and other male genital system). In addition, because breast cancer is predominantly a female cancer and we observe in our population only up to three cases per year in males, we also excluded male breast cancer from the analysis. Gender-specific cancer sites contribute, of course, to overall cancer incidence and cancer survival. But in order to analyse whether women share better survival than men, it is in our opinion best to restrict the analysis to cancer sites occurring in both sexes in order to have comparable settings. In the analysis for all cancer sites combined in one group, we also adjusted for case mix.

Gender difference in survival was modelled using a relative excess risk model (RER).[17] In a first step, relative survival rates are computed using a stata procedure strs provided by Paul Dickman.[18] These relative survival rates are then modelled using a generalized linear model. In more formal terms: the hazard-function $\lambda(t,x)$ for a patient with characteristics x at time t is estimated as the sum of a baseline hazard $\lambda^*(t,x)$ and a so-called excess hazard $\nu(t,x)$. It is assumed that the excess hazard is a product of covariates x_1 to x_n, here written as $\exp(x\beta)=e^{x\beta}$. This means:

$$\lambda(t,x) = \lambda^*(t,x) + e^{x\beta} = \lambda^*(t,x) + e^{\beta_0+\beta_1 x_1+\ldots+\beta_n x_n}. \quad (1)$$

We applied the Hakulinen–Tenkanen model using the stata code proposed by Paul Dickman.[18] For all models, we included follow-up time in the model, and the analysis was restricted to the first 5 years of follow-up because it is usually inappropriate to assume proportional hazard assumption on longer follow-up periods. All relative excess risks given by the respective RER model are for women compared to men as the reference group. For short, we use the notation RER for women. Models were built separately for every cancer site. We started with a kind of full model with terms for gender, year of follow-up, four age categories, two period categories, stage and histological verification. Cases with stage unknown remained in the analysis, whereby unknown stage was explicitly categorized. We then dropped terms if they were not statistically significant; significance was tested using the likelihood ratio test. Afterwards, if model fit was not good, we added interaction terms if the respective term had a statistically significant effect. Model fit was assessed by deviance and Pearson residuals, divided by degrees of freedom. Confidence intervals (CIs) for estimators were computed based on standard errors given by observed information matrix, the standard Stata option.

Data on life expectancy were provided in routine statistics published by Statistics Austria and the Department of Statistics in Tyrol.

All computations were performed with Stata Version 9.[19]

Results

In the following paragraphs, we describe in brief some basics of patient characteristics for every cancer site investigated. Details of patient characteristics are given in table 1 and univariate and multivariate relative risks with information on model fit in table 2.

We analysed a total of 941 head and neck cancer cases (without larynx), one-quarter of which were in women; see table 1. Mean age was 60 years and there were only small differences in age structure. There are distinct differences in staging distribution: the proportion of early Stage I was 18% for women and 13% for men and the proportion of Stage IV was 20% for women and 38% for men. RER for women was 0.57 in univariate analysis and 0.72 (95% CI 0.56–0.93) in multivariate analysis, see table 2.

We analysed a total of 2418 stomach cancer cases, 47% of which were in women; see table 1. Female cases were older in the mean (72 vs. 69). We found no differences in staging distribution. RER for women was 0.97 in univariate analysis and 0.86 (95% CI 0.75–0.97) in multivariate analysis, see table 2.

We analysed a total of 4519 colorectal cancer cases, half of which were in women (51%); details are shown in table 1. Female cases were older in the mean (71 vs. 67). RER for women was 1.16 in univariate analysis and 1.06 (95% CI 0.95–1.18) in multivariate analysis; see table 2.

We analysed a total of 951 pancreatic cancer cases, slightly more than half of which were in women (54%); details are shown in table 1. Female cases were older in the mean (73 vs. 67). About one-third of cases had no staging information; Stage IV accounted for 44% of men and 37% of women. RER for women was 1.06 in univariate analysis and 0.96 (95% CI 0.78–1.19) in multivariate analysis; see table 2.

We analysed a total of 3742 lung cancer cases, about one-quarter of which were in women (26%); details are shown in table 1. There were only minor differences in age structure. We observed only small differences in staging distribution, however for one-quarter of the cases stage was unknown. RER for women was 0.87 in univariate analysis and 0.82 (95% CI 0.75–0.90) in multivariate analysis; see table 2.

We analysed a total of 1670 bladder cancer cases, about one-quarter (28%) being in women; details are shown in table 1. There were some differences in age distribution; mean age was 71 years for women and 69 years for men. We observed distinct differences in staging distribution: the proportion of early Stage I was 49% for women and 61% for men, the proportion of Stages III and IV was 15% for women and 11% for men, and the proportion of cases whose stage was unknown was 19% for women and 13% for men. RER for women was 1.57 in univariate analysis and 1.13 (95% CI 0.88–1.46) in multivariate analysis; see table 2.

We analysed a total of 1264 kidney cancer cases, 42% of which were in women; see table 1. There were differences in age distribution: mean age was 68 years for women and 63 years for men. We observed no differences in staging distribution. RER for women was 1.18 in univariate analysis and 1.19 (95% CI 0.93–1.53) in multivariate analysis; see table 2.

We analysed a total of 1607 melanomas, with a slight predominance in women (54%); details are shown in table 1. There were no differences in age distribution and no differences in staging distribution: ~90% of cases were Stages I and II, 5–8% Stages III and IV and 4% had no staging information. RER for women was 0.92 in univariate analysis and 0.85 (95% CI 0.55–1.31) in multivariate analysis, see table 2.

We analysed a total of 752 thyroid cancer cases, three-quarters of which were in women; see table 1.

There were some differences in age structure: mean age was 53 years for women and 55 years for men. We observed differences in staging distribution: the proportion of Stages I and II was 69% in women and 59% in men and of Stages III and IV 22% in women and 28% in men. RER for women was 0.70 in univariate analysis and 0.74 (95% CI 0.42–1.30) in multivariate analysis; see table 2.

For all solid cancer sites combined, we analysed 21 102 cases, 42% of which were in women; details are shown in table 1. Women were slightly older, mean age being 67 years for women and 65 years for men. There were only slight differences in staging distribution for all sites combined. RER for women was 0.91 in the univariate analysis, 0.88 (95% CI 0.84–0.91) in the multivariate analysis without adjusting for case mix and 0.95 (95% CI 0.91–0.99) after adjusting for case mix. If the analysis was broken down by age group, univariate RER for women was 0.67, 0.81, 0.93 and 1.07, multivariate RER for women without adjusting for case mix was 0.81 (95% CI 0.76–0.89), 0.78 (95% CI 0.71–0.84), 0.91 (95% CI 0.84–0.99) and 1.07 (95% CI 0.96–1.19) and multivariate RER for women after adjusting for case mix 0.95 (95% CI 0.87–1.04), 0.84 (95% CI 0.77–0.92), 0.95 (95% CI 0.88–1.03) and 1.10 (95% CI 0.98–1.22) for age groups 20–59, 60–69, 70–79 and ≥80, respectively. For details see table 3 and figure 1.

Table 1 Patient characteristics

Site	*N*		Percent	Mean age
Head and neck (without larynx) [C00–C14, C30–C31]	941	Women	26	60
		Men	74	59
Stomach [C16]	2418	Women	47	72
		Men	53	69
Colorectum [C18–C21]	4519	Women	51	71
		Men	49	67
Pancreas [C25]	951	Women	54	73
		Men	46	67
Lung [C33–C34]	3742	Women	26	66
		Men	74	65
Bladder [C67]	1670	Women	28	71
		Men	72	69
Kidney [C64–C66, C68]	1264	Women	42	68
		Men	58	63
Melanoma [C43]	1607	Women	54	54
		Men	46	54
Thyroid [C73]	752	Women	74	53
		Men	26	55
All solid sites (except NMSC) [C00–C80, except C44 and C50–C63]	21 102	Women	42	67
		Men	58	65

Discussion

Our main objective was to investigate whether survival differs between women and men in the population of Tyrol. Using the incidence data set for Tyrol, we applied a RER model that adjusts for main factors. The analysis was conducted for the main solid cancer sites and for the combination of all solid cancer sites in total and was split according to age class.

Most of our site-specific results are in line with published results, see for example.[2–5,20–22] We observed poorer survival for women only for colorectal cancer, bladder cancer and kidney cancer, with none of these results being statistically significant. For colorectal cancer, our finding of a non-significant RER (1.06) does not stand in contradiction to published studies, see for example.[4,5] A publication bias might have prevented non-significant results from being published, whereas we analysed and report results on all solid cancer sites with an adequate number of cases.

For bladder cancer, we obtained a multivariate RER of 1.13 for women without statistical significance. Recent analysis by Mungan *et al.*[20] showed poorer survival for women in the SEER (significant) and also in the Netherlands (non-significant) data set. However, the results differed for Stage I (better survival for women) and Stages II and IV (poorer survival for women). Micheli *et al.*[2,3] also found poorer survival for women. Therefore, for bladder cancer, there seems to be some tendency towards poorer survival in women. However, there are well-recognized differences in the classification and registration of tumours that are recorded as malignant by some cancer registries and as non-malignant (benign) by others.[23]

For aggregation of all cancer sites combined, we separately fitted a model instead of aggregating site-specific results. This procedure thus indirectly adjusted for differences in site mix between women and men.

For all cancer sites combined, the lesser excess mortality for females is 0.88 without adjusting for case mix and 0.95 after adjusting for case mix. This result is identical to a recent analysis by Micheli *et al.*[3] on the large EUROCARE-4 data set. However, Micheli *et al.* observed a rather homogeneous gradient from a larger difference for younger age groups to a minor difference for older age groups. Our results do not show this homogeneous gradient and we observe a tendency towards worse survival for females in age group ≥80 years. Part of these differences can be explained by the distribution of sites by age groups in our data: whereas for younger females, the proportion of sites with better survival for females compared to males is larger then 55%, this proportion reduces to about one-third for women aged ≥80 years and in contrast the proportion of, for example, colorectal cancer with an insignificant RER of 1.06 increases from 17% to 32% (data not shown).

Table 2 RER estimators for solid cancer sites (univariate and multivariate relative risk and information on model fit)

Site	Univariate RER[a] with 95% CI	Multivariate RER[a] with 95% CI	Variables in model[b]	Model FIT[c]
Head and neck	0.57 (0.44–0.75)	0.72 (0.56–0.93)	Age, Stage	1.04/0.98
Stomach	0.97 (0.87–1.08)	0.86 (0.75–0.97)	Age, Stage, Period, Fup*Stage	1.12/1.01
Colorectum	1.16 (1.04–1.29)	1.06 (0.95–1.18)	Age, Stage, Period, HV, Fup*Stage	1.12/1.00
Pancreas	1.06 (0.92–1.23)	0.96 (0.78–1.19)	Age, Stage, Period, HV, Fup*Stage	1.23/1.15
Lung	0.87 (0.80–0.95)	0.82 (0.75–0.90)	Age, Stage, Period, HV, Fup*Stage	1.21/1.07
Bladder	1.57 (1.23–2.00)	1.13 (0.88–1.46)	Age, Stage, Period, HV, Fup*Stage	0.98/1.00
Kidney	1.18 (0.92–1.50)	1.19 (0.93–1.53)	Age, Stage. HV, Fup*Stage	1.20/1.13
Melanoma	0.92 (0.57–1.49)	0.85 (0.55–1.31)	Age, Stage, Fup*Stage	0.99/0.90
Thyroid	0.70 (0.40–1.23)	0.74 (0.42–1.30)	Age	1.06/0.81

a: For women compared to men

b: Year of follow-up (Fup) is always in model, also in univariate model; Fup*Stage, interaction term for follow-up and stage; HV, histological verification; Period, year of diagnosis

c: Deviance divided by degrees of freedom and Pearson divided by degrees of freedom

Factors that explain the observed differences between women and men under discussion are differences in tumour cell biology, which could be influenced by reproductive hormones,[21] differences in anatomical situation, for example, for bladder cancer[20] and melanoma,[22] and possibly most importantly differences in risk factors, especially comorbidity combined with smoking-related cancers. It is well known that about 3 of 10 cancer cases can be attributed to smoking and that smoking increases general mortality.[24] Relative survival adjusts for differences in background mortality, however, does not adjust for differences in mortality between smokers and non-smokers. Cancer registries usually contain no information on smoking habits of patients. Therefore, it would be very interesting to estimate the effect that differences in smoking prevalence between women and men have on the survival difference we observed.

Strengths and limitations

The following paragraphs will deal with the strengths and limitations of our study. One of the strengths of our study is that it employs a population-based data set, thus analysing all cancer patients in the whole population, because we know that trial patients are often a prognostically favourable subset of all patients.[25] The incidence data set for Tyrol has been published in Cancer Incidence in Five Continents since 1988, which is an indirect measure of good completeness.

The next question is whether the model we applied is well-suited to answer our question. First, in survival analysis for oncological patients, it is state of the art to adjust for baseline mortality by applying relative survival. Therefore, relative survival is applied, for example, to compare survival figures in various countries.[8,9] It is also well known that women and men have distinct life expectancy and mortality rates. Therefore, in order for a comparison of survival between women and men to be valid it is essential to adjust for differences in life expectancy. The model we applied is based on relative survival rates and, as such, should adequately adjust for that difference.

Summarizing, the main strengths are that the model we applied seems to be appropriate and the survival data are valid.

We are, of course, faced with some limitations. Cancer registries usually have only limited data for controlling information biases. If we compare survival for women and men, it is necessary to adjust for factors influencing survival. We noted in the 'Results section' that for some cancer sites like stomach, colorectum, pancreas and kidney, women are older than men at time of diagnosis. Also, some sites show clear differences in staging distribution. Our model adjusts for these few factors. However, residual confounding could be a limiting factor. Whether gender has a direct effect on survival, whether the effect is confounded in a classical way by, for example, tumour stage or whether the effect is influenced by some unknown factor interacting with tumour stage and with survival needs to be discussed; see for example Cole and Hernan.[26]

It is also possible that a change occurred over time in factors influencing survival differences. Access to the medical system in Austria was already free of charge in the 1980s and 1990s. However, the social situation of women has changed greatly in the last three decades with a transition occurring from a very traditional female role to women holding a position in modern society. We cannot rule out the possibility that these changes influenced survival figures.

Table 3 RER estimators for all solid cancer sites except NMSC combined (univariate and multivariate relative risk)

Age (years)	*N* (% female)	Univariate RER[a]	Multivariate[b] RER[a] without adjusting for case mix with 95% CI	Multivariate[b] RER[a] after adjusting for case mix with 95% CI
All	21 102 (42%)	0.91	0.88 (0.84–0.91)	0.95 (0.91–0.99)
20–59	6547 (39%)	0.67	0.81 (0.76–0.89)	0.95 (0.87–1.04)
60–69	5395 (34%)	0.81	0.78 (0.71–0.84)	0.84 (0.77–0.92)
70–79	5680 (45%)	0.93	0.91 (0.84–0.99)	0.95 (0.88–1.03)
≥80	3480 (57%)	1.07	1.07 (0.96–1.19)	1.10 (0.98–1.22)

a: For women compared to men
b: Adjusted for age, stage, year of diagnosis, histological verification and interaction terms for follow-up and stage and follow-up and age; year of follow-up (Fup) is always in model, also in univariate model

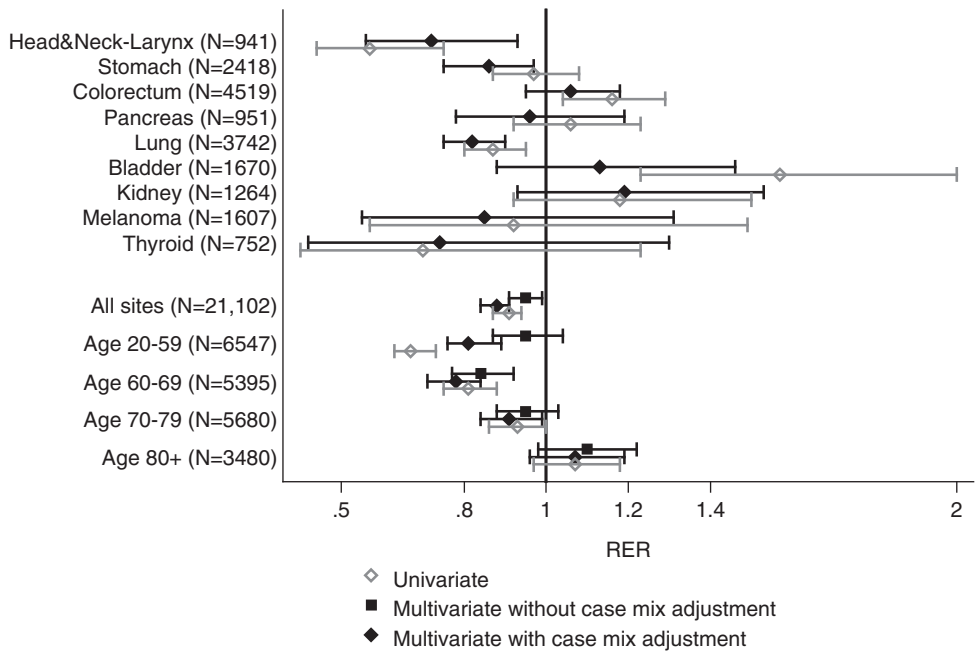

Figure 1 Gender effects for solid cancer sites and all sites combined by age class: gender RER with 95% CIs. RER estimates are shown for women compared to men as the reference group

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Conflicts of interest: None declared.

Key points

- In a healthcare system with free access to diagnostics and therapy, female cancer patients have a lesser excess mortality risk than do men for lung, stomach and head and neck cancer sites after adjusting for staging distribution and for all sites combined after also adjusting for case mix.
- Every cancer registry's report should routinely break down all results for gender.
- When analysing gender differences in survival, differences in life expectancy must be considered.

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