Coming of age : treatment and outcomes in older patients with breast cancer

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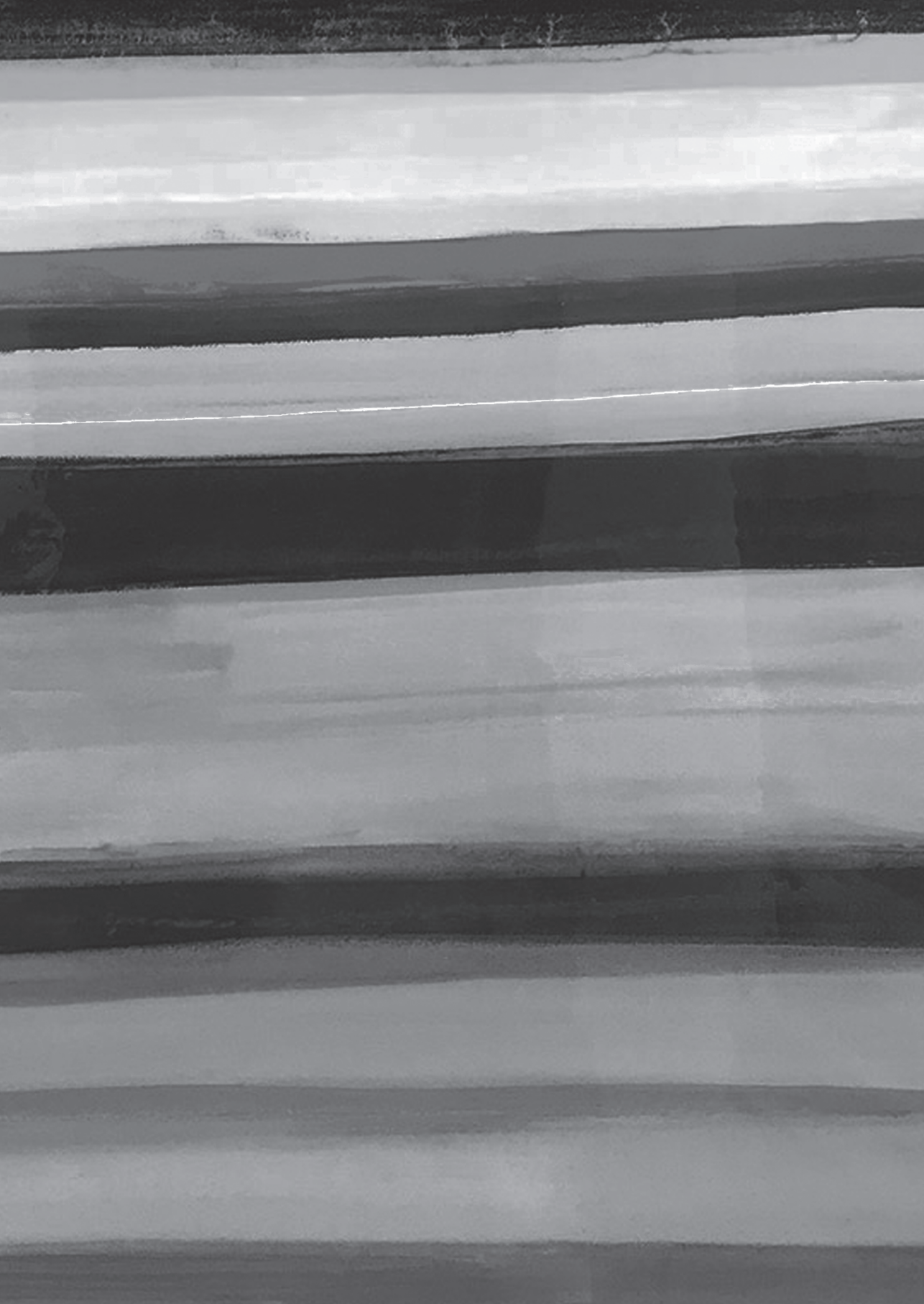

CHAPTER 8

Reporting absolute risks in observational studies: data from the TEAM-study on breast cancer

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ABSTRACT

Reporting absolute risks in survival analysis for main endpoints and subgroups have been recommended by the STROBE and CONSORT guidelines but too often this recommendation is neglected. Clinical studies often use the Cox proportional hazard regression model to estimate effect sizes and to adjust for confounders. This may explain why there is a predominance for reporting relative risks in clinical studies. In this article, we present the Aalen additive hazards model, a less well known but easy to apply additive survival model to calculate absolute risks. This model directly estimates absolute risk differences and provides the opportunity to include covariates in the model, to address confounding factors and test for interaction, similar to the Cox proportional hazards model. As an example, we use data from the Tamoxifen Exemestane Adjuvant Multinational (TEAM) study to report on the effect of age on breast cancer related mortality in absolute risks using the Aalen additive hazards model and relative risks using the Cox proportional hazards model. We discuss the interpretation of both risk estimates and demonstrate that the effect of age on breast cancer mortality among subgroups changes depending on the relative or absolute model. We conclude that the additive hazards model is more representative for clinical practice and provides a better interpretation of the impact of age on breast cancer mortality for clinicians and patients.

INTRODUCTION

Most clinical papers report on effect sizes of exposures and treatments as relative risks, reinforcing the strength of the (causal) relation.[1,2] However, for an individual the interpretation of a relative risk is ambiguous, as the absolute risk is not taken into account.[3] Earlier we reported that among women who suffer from breast cancer, those 75 years or older were at a 1.63-fold higher risk to die from cancer compared to women younger than 65 years.[4] The question that immediately that is immediately raised is; '1.63 times *what*?'. The key question for an older patient is whether she should be worried about this increased likelihood to die from breast cancer, and for the treating physician it is essential to ascertain whether additional treatment would be effective to reduce the risk with resultant significant clinical benefit.

When reporting the impact of a clinical intervention, the Number Needed to Treat (NNT) and Number Needed to Harm (NNH) are commonly used composite estimates that integrate information on both the absolute risk and the relative change of that risk. Observational studies report on the natural history of the disease and not primarily on outcomes of an intervention. For this reason it is counter-intuitive to report on the impact of risk factors as the number needed to treat, or to harm. The 'STrengthening the Reporting of OBservational studies in Epidemiology' (STROBE) consensus report recommends reporting outcomes as both relative and absolute measures of effect.[5] It is sobering that despite these sound methodological arguments effect sizes in observational studies are almost exclusively reported as relative risks serving the etiologic interpretations of the findings but not the clinical impact on individuals.[1]

Observational studies often rely on survival analyses and use Cox *proportional* hazard regression to correct for confounding factors.[6] This preferred choice of methods may explain why there is a predominance for reporting relative risks in observational studies. There is however no methodological barrier for applying alternative models that regress *additional* hazards and allow for entering additional covariates to adjust for confounding. Here, we present the Aalen additive hazards model, a less well known but easy to apply additive survival model to calculate absolute risks. Similar to the Cox proportional hazards model, this model directly estimates absolute risk differences and provides the opportunity to include covariates in the model, address confounding factors and test for interaction.[7] We present an example from the Tamoxifen Exemestane Adjuvant Multinational (TEAM) study reporting on the effect of age on breast cancer mortality in absolute risks next to standard relative risks to enable a better understanding of the clinical impact. Furthermore, we provide a short tutorial introducing programming this model in the R statistics software.

METHODS

Data

The TEAM study was designed as a randomized controlled trial including postmenopausal patients with estrogen receptor and/or progesterone positive breast cancer. Patients were included between January 2001 and January 2006 and randomized to receive exemestane for five years, or a sequential treatment regimen of tamoxifen followed by exemestane for a total of five years. Further details of this study are extensively described elsewhere.[8] After five years of follow up there were no differences in any of the primary end points between the two treatment arms,[8] and thereafter the total cohort is used for observational research into exploring determinants for, and outcomes of breast cancer.

For the present analysis, patients were categorized in three categories of age at diagnosis (< 65 years, 65-74 years and ≥ 75 years).[9] First, the effect of age on mortality from breast cancer was examined in the complete cohort of patients. Second, the effect of age was examined in subgroups of patients with specific prognostic markers of breast cancer mortality, i.e. tumor size and lymph node status.[10] Tumor size was divided into two categories: < 2 cm and ≥ 2 cm whereas lymph node status was defined as negative (no regional lymph node metastasis) or positive (one or more positive regional lymph nodes). The follow-up was defined as the time from inclusion in the study to death from breast cancer, death from other causes or time of censoring at the end of follow-up. Cause of death was indicated on a case report form and categorized into ten pre-specified groups and verified by the central datacenter. If a patient was diagnosed with metastatic breast cancer prior to or at time of death, cause of death was categorized as death from breast cancer.

Survival models

Time to event models estimate the probability of experiencing an event in the next unit of time. The so-called hazard at time *t* can be modelled either on a relative (multiplicative) or an absolute (additive) scale. For the present analyses, we applied the most commonly used multiplicative (Cox) and additive survival model (Aalen).[7] Both models include a baseline hazard, which follows a non-parametric time-dependent function. The Cox proportional hazards model than estimates on - a multiplicative scale - the increase of the hazard in the group of interest when compared to the hazard in the reference group. This is referred to as the hazard ratio (HR) and estimates a proportional measure of the strength of the relation. In the Aalen model, the additional hazard in the group of interest is modelled as a linear function on the unspecified baseline hazard of the reference group and when applied to human cohorts the resulting effect estimates (β) can directly be interpreted as the additional number of people experiencing the event per unit of time. Both models allow for adding additional covariates to correct for confounding. Taken together, the Aalen additive model

represents an additive semi-parametric technique for survival analysis that is at least as flexible as the Cox model.

Statistical and computational aspects

The statistical software programme R has the package "timereg" which has extensive capabilities for estimating and analyzing additive hazard models and is easily applicable for researchers who are familiar with the software.[7,11] For those unfamiliar with the R software, a tutorial for using the model is provided in the supplemental materials. We studied the effect of age on mortality from breast cancer in the complete cohort and subgroups of patients with specific prognostic disease characteristics. To this end, we used the Cox proportional hazard regression to estimate hazard ratio's, and estimated the absolute risk difference in mortality from breast cancer using the Aalen additive hazard regression. Hazard ratios indicated the relative increase of mortality when compared to the reference group whereas risk differences are presented as the additional number of deaths per 1000 person years. As potential confounders we included country, histological grade, tumor stage, lymph node status, progesterone receptor status, most extensive surgery, radiotherapy, chemotherapy and endocrine therapy. Interaction as deviation from relative effects in the Cox proportional hazards model and interaction as deviation from absolute effects in the Aalen additive model were tested.

All statistical tests were two-sided and P-values of less than 0.05 were considered statistically significant. Proportional differences were compared using a Pearson χ^2 test. Median follow up and interquartile range (IQR) were calculated using the reversed Kaplan Meier estimate.[12] All analyses were performed in R Software (version 3.0.0) using the "survival" and "timereg" packages.[13]

RESULTS

9766 women diagnosed with breast cancer were included in the TEAM study; 5349 were younger than 65 years, 3060 patients were aged 65 to 74 years and 1357 patients were aged 75 years or older. Table 1 shows baseline characteristics at time of diagnosis for the three age groups separately. Median follow-up was 5.1 years (IQR 4.1-5.9).

Increasing age was associated with a higher risk of dying from breast cancer; cumulative mortality from breast cancer at five years increased from 5.1% in patients younger than 65 years, to 5.8% in patients aged 65 to 74 years and 8.3% in patients aged 75 ≥ years (Table 2). Five years after inclusion, patients aged ≥ 75 years at baseline were at a 1.7-fold higher risk of dying from breast cancer than patients aged under 65 years, in absolute numbers this corresponds to an additional number of 6.2 deaths from breast cancer per 1000 patient years.

Table 1 Patient characteristics by age at diagnosis

	< 65 years n=5349		65-74 years n=3060		≥ 75 years n=1357		
	n	%	n	%	n	%	*P* value
Histological grade and differentation							0.065
G1, well	911	17.0	550	18.0	216	15.9	
G2, moderate	2581	48.3	1537	50.2	679	50.0	
G3, G4, poor	1377	25.7	732	23.9	329	24.2	
Unknown	480	9.0	241	7.9	133	9.8	
Tumor size (cm)							<0.001
< 2	3298	61.7	1806	59.0	593	43.7	
≥ 2	2037	38.1	1247	40.8	764	56.3	
Unknown	14	0.3	7	0.2	0	0.0	
N stage							0.117
Negative	2800	52.3	1623	53.0	690	50.8	
Positive	2518	47.1	1418	46.3	651	48.0	
Unknown	31	0.6	19	0.6	16	1.2	
Estrogen receptor							<0.001
Positive	5219	97.6	3022	98.8	1344	99.0	
Negative	128	2.4	35	1.1	13	1.0	
Unknown	2	0.0	3	0.1	0	0.0	
Progesterone receptor							0.534
Positive	4029	75.3	2268	74.1	1004	74.0	
Negative	915	17.1	554	18.1	255	18.8	
Unknown	405	7.6	238	7.8	98	7.2	
Country							<0.001
The Netherlands	1428	26.7	852	27.8	473	34.9	
Germany	871	16.3	454	14.8	146	10.8	
United Kingdom/Ireland	696	13.0	413	13.5	166	12.2	
Greece	110	2.1	71	2.3	26	1.9	
France	722	13.5	403	13.2	105	7.7	
United States	1159	21.7	695	22.7	378	27.9	
Japan	98	1.8	66	2.2	20	1.5	
Belgium/Luxembourg	265	5.0	106	3.5	43	3.2	
Most extensive surgery							<0.001
Mastectomy	2120	39.6	1372	44.8	841	62.0	
Wide local excision	3223	60.3	1685	55.1	515	38.0	
Unknown	6	0.1	3	0.1	1	0.1	
Radiotherapy							<0.001
Yes	3980	74.4	2030	66.3	687	50.6	
No	1331	24.9	994	32.5	651	48.0	
Unknown	38	0.7	36	1.2	19	1.4	
Chemotherapy							<0.001
Yes	2742	51.3	700	22.9	71	5.2	
No	2607	48.7	2357	77.0	1284	94.6	
Unknown	0	0.0	3	0.1	2	0.1	
Endocrine therapy							0.384
Tamoxifen followed by exemestane	2667	49.9	1546	50.5	655	48.3	
Exemestane	2682	50.1	1514	49.5	702	51.7	

When stratified for tumor size, cumulative mortality from breast cancer at five years was higher in the older age groups, both in patients with small and large tumors (Table 2). Among patients with small tumors, mortality from breast cancer was 2.0-fold higher in patients aged over 75 years when compared to those under 65 years, while among patients with large tumors a similar age difference associated with a 1.6-fold increased mortality risk. A comparison of these relative risks suggests that the effect of increasing age is less strong in patients with larger tumors. On an absolute scale however, this age difference corresponds to an additional number of 5.1 deaths per 1000 patient years in patients with small tumors, whereas there was an additional number of 9.0 deaths per 1000 patient years in patients with large tumors. Apparently, the impact of increasing age is more pronounced in patients with larger tumors.

When stratified for lymph node status, cumulative mortality from breast cancer at five years was higher in the older age groups, both in patients with negative and positive lymph node status (Table 2). Among patients with a negative lymph node status, older age was associated with a 1.7-fold increased risk of dying from breast cancer and this was not different for patients with a positive lymph node. These relative risk estimates suggest that the effect of increasing age on mortality from breast cancer is not dependent on lymph node status. On an absolute scale however, the corresponding absolute risk differences were an additional number of 3.1 deaths per 1000 patient years in patients with lymph node negative disease, whereas there was an additional number of 10.8 deaths per 1000 patient years in those with lymph node positive disease. Apparently, the impact of increasing age is more pronounced in patients with a positive lymph node status.

Figure 1A presents a forest plot of the age specific relative risks of mortality from breast cancer when all patients were analyzed as one group and in subgroups stratified for tumor size and lymph node status. Comparing the relative risks from top to bottom, the age specific risk estimates are similar in the whole group when compared to the risk estimates in strata of tumor size and lymph node status. The comparison of the relative risks does not provide arguments for effect modification. Statistical testing for interaction provided p-values of 0.85 for tumor size and 0.99 for lymph node status respectively.

Figure 1B presents a forest plot of the age specific risk differences in mortality from breast cancer when all patients were analyzed together, and in subgroups separately. Comparing the risk differences from top to bottom, the age specific risk differences are smaller in those with smaller tumors and in those with a negative lymph node status. The risk differences are largest in those with a positive lymph node status. Statistical testing for interaction provided p-values of 0.14 for tumor size and 0.05 for lymph node status respectively.

Table 2 Incidence, relative risk and risk difference for breast cancer related mortality stratified for age, tumor size and lymph node status

			Incidence	**Relative Risk***		**Risk Difference***	
	Age	Numbers of events/ numbers at risk	Cumulative Mortality at five years (95% CI)	Hazard Ratio (95% CI)	P-value	Additional deaths per 1000 person years (95% CI)	P-value
All							
	< 65	279/5349	5.1 (4.5-5.8)	1.00		0	
	65-74	179/3060	5.8 (4.8-6.7)	1.24 (1.01-1.52)	0.040	1.55 (-0.63-3.73)	0.0867
	≥ 75	110/1357	8.3 (6.6-9.9)	1.73 (1.33-2.26)	<0.001	6.19 (2.52-9.86)	<0.001
Tumor size							
< 2 cm	< 65	96/3298	2.9 (2.3-3.6)	1.00		0	
	65-74	55/1806	3.1 (2.2-4.0)	1.23 (0.86-1.76)	0.378	0.71 (-1.27-2.69)	0.486
	≥ 75	28/593	3.6 (1.9-5.2)	2.03 (1.25-3.30)	0.004	5.06 (0.71-9.41)	0.026
≥ 2 cm	< 65	182/2037	8.8 (7.4-11.1)	1.00		0	
	65-74	123/1247	9.6 (7.7-11.4)	1.22 (0.94-1.57)	0.129	3.61 (-1.37-8.59)	0.155
	≥ 75	82/764	12.0 (9.3-14.6)	1.58 (1.15-2.18)	0.004	9.03 (2.37-15.69)	0.006
P-value for interaction				0.85		0.14	
Lymph node status							
Negative	< 65	72/2800	2.6 (1.9-3.2)	1.00		0	
	65-74	44/1623	2.8 (1.9-3.7)	1.10 (0.75-1.66)	0.660	-0.06 (-2.06-1.94)	0.952
	≥ 75	28/690	4.2 (2.5-6.0)	1.73 (1.07-2.82)	0.026	3.05 (-0.71-6.81)	0.113
Positive	< 65	206/2518	7.9 (6.8-9.1)	1.00		0	
	65-74	135/1418	9.1 (7.4-10.7)	1.25 (0.98-1.58)	0.072	3.99 (-0.32-8.30)	0.070
	≥ 75	80/651	12.3 (9.4-15.1)	1.71 (1.25-2.34)	<0.001	10.76 (3.74-17.76)	0.003
P-value for interaction				0.99		0.05	

* adjusted for the following confounders: country, histological grade, tumor stage, lymph node status, progesterone receptor status, most extensive surgery, radiotherapy, chemotherapy and endocrine therapy

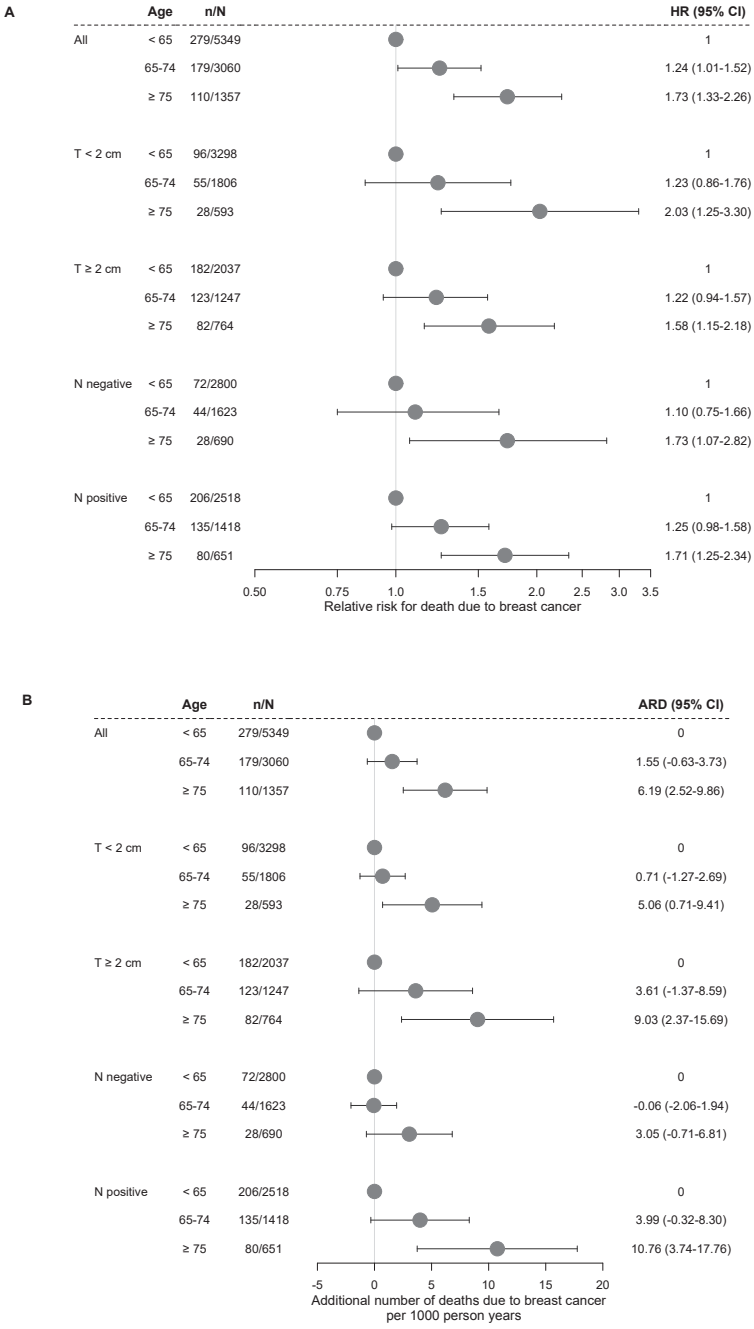

Figure 1 Forrest plots presenting relative risks and absolute risks of dying from breast cancer
A) Relative risk of dying due to breast cancer by age group in all patients and by tumor size and lymph node status B) Additional number of deaths (per 1000 person years) of dying due to breast cancer in all patients and by tumor size and lymph node status

DISCUSSION

Using the outcomes of a large cohort of women with breast cancer, we show that the relative risk of dying from breast cancer increases with increasing age. The relative risk increase is similar for those with favorable and unfavorable prognostic characteristics, erroneously suggesting that the impact of increasing age is independent of prognosis. At the same time, we show that the additional number of older women who die from breast cancer is higher among women with a poor prognosis when compared to those with a good prognosis. This extra number of patients (per unit of time) affected by the risk factor under study incorporates both the baseline risk (or hazard) and relative risk increase (or hazard ratio) and thus provides a better estimate of the clinical impact.

Clinicians prefer to target patients for whom the clinical impact of an intervention will be high. Although this may appear very straight forward, this crucial piece of information is lost when reporting relative risk estimates only. A significant age interaction was observed between lymph node negative and lymph node positive status in the additive model, while this interaction was not observed in the relative model. Indeed, it is well-known that proving statistical interaction depends on the underlying scale of the measurement.[14] When only relative risk measures would have been reported, clinicians may have concluded that the effect of age is not depending on the lymph node stage. However, when also presenting risk differences the clinical perspective changes: the significant age interaction that was observed indicates that older age inflicts more harm in patients with lymph node positive disease. It may urge clinicians to specifically address additional interventions in older patients with a more severe stage of disease.

Reporting risk differences together with relative risks will increase the understanding of clinical impact of effect sizes found in observational studies and will help target subgroups who benefit most from interventions. For no obvious reason, the Aalen additive model that we have applied here, has not been applied frequently in medical research. The appendix provides the codes how to program the analyses in R. In line with our findings, other scholars who applied the Aalen model made clear that comparing the difference in absolute risk gave rise to new perspectives on effect the effect of risk factors or interventions when compared to reporting relative risks only.[3,15,16]

In cohort studies, absolute outcomes are most often reported as cumulative incidences. Although they provide a relevant estimate of absolute effect, there is no possibility to account for confounding variables. As shown in this paper, the additive hazard model, as any other regression model, provides the opportunity to include covariates in the model and to address confounding factors. Furthermore, the possibilities to test for statistical

interaction are similar to the Cox proportional hazards model. Last, absolute effect of risk factors within subgroups can easily be visualized using traditional forest plots to further improve the understanding of the findings. It is sobering that the outcome produced by the Aalen additive model, the additional number of people affected per unit of time, is not yet embraced with enthusiasm.

In conclusion, we have presented an easily applicable model to estimate absolute effect measures in time to event analysis while preserving the possibility to adjust for confounders and test for statistical interaction. We have shown that interpretation of effect of risk factors among subgroups can change depending on the relative or absolute scale of the effect measure due to variation in underlying baseline risk. This should be taken into account when evaluating clinical impact of risk factors.

Cooperative investigators of the TEAM study

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