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Breast cancer survival and season of surgery: an ecological open cohort study

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We will be pleased to share the necessary data for the statistical review of our paper. However, it is not possible for us to make the entire data material public available.

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ABSTRACT

Background: Vitamin D has been suggested to influence the incidence and prognosis of breast cancer, and studies have found better overall survival (OS) after diagnosis for breast cancer in summer–autumn, where the vitamin D level are expected to be highest.

Objective: To compare the prognostic outcome for early breast cancer patients operated at different seasons of the year.

Design: Open population-based cohort study.

Setting: Danish women operated 1978–2010.

Cases: 79 658 adjusted for age at surgery, period of surgery, tumour size, axillary lymph node status and hormone receptor status.

Statistical analysis: The association between OS and season of surgery was analysed by Cox proportional hazards regression models, at survival periods 0–1, 0–2, 0–5 and 0–10 years after surgery. A two-sided p value <0.05 was considered statistical significant.

Results: Only after adjustment for prognostic factors that may be influenced by vitamin D, 1-year survival was close to significantly associated season of surgery. 2, 5 and 10 years after surgery, the association between OS and season of surgery was not significant.

Limitations: Season is a surrogate measure of vitamin D.

Conclusions: The authors found no evidence of a seasonal variation in the survival after surgery for early breast cancer. Lack of seasonal variation in this study does not necessarily mean that vitamin D is of no importance for the outcome for breast cancer patients.

ARTICLE SUMMARY

Article focus

- Breast cancer survival and season of surgery.

Key message

- No evidence of a seasonal variation.

Strengths and limitations of this study

- The sample size (approximately 80 000 cases).
- The population-based approach in a limited geographic area.
- The prospectively collected characteristics of tumour and lymph node status.
- The long follow-up (median 10.0 years).
- The lack of information about vitamin D status in the individual patient at the time of surgery.
- It is not known whether vitamin D levels of the breast cancer patients follow that of the background population.

INTRODUCTION

Over the past decades, ecological studies have inspired to the hypothesis that exposure to sunlight and hence difference in serum vitamin D may influence both risk and prognosis for breast cancer.[1 2] The hypothesis has been supported by several in vitro and animal studies,[3 4] in addition to case–control and cohort studies with measurements of vitamin D as serum 25 hydroxy-vitamin D (25 (OH)D),[5–15] although not all studies including two meta-analyses could support these findings.[16–19] Four studies found the prognosis of breast cancer to vary with the season for diagnosis. The three of them found that patients diagnosed in summer–autumn had a better disease outcome than those diagnosed in winter–spring,[20–22] and one study found a higher overall mortality for patients diagnosed in late summer compared with those diagnosed in mid-winter.[23]

In Denmark, positioned at 55–58° northern latitude, there is no sufficient sun to synthesise vitamin D in the human skin during 6–8 months of the year. Measurements of vitamin D in healthy Danish volunteers demonstrate a pronounced seasonal variation of vitamin D with a maximum in late summer and a minimum in early spring, which indicates that the content of vitamin D in the average Danish diet could not compensate for the lack of sun-induced vitamin D production during wintertime.[24]

If the vitamin D status at the time of the operation is important for the overall survival (OS), it should be both easy and inexpensive to adjust preoperatively. The aim of this study is to compare the prognostic outcome for early breast cancer patients diagnosed and operated at different seasons of the year based on a large population-based registration of women with breast cancer in

Denmark including detailed information on prognostic factors.

MATERIALS AND METHODS

The Danish Breast Cancer Cooperative Group (DBCG) founded in 1977 is a population-based registry, which collects data on almost all cases of invasive breast cancer among residents in Denmark (a population of 5.5 million, emigration and immigration rates <2%) (http://www.dst.dk). Virtually, all involved Danish hospital departments have applied DBCG's guidelines for diagnostic procedures, surgery, radiotherapy, adjuvant systemic therapy and follow-up for early breast cancer. Diagnostic, therapeutic and follow-up data have been accumulated prospectively in the DBCG registry by the use of standardised forms. The DBCG Data Center applied the same procedures for all patients, including monitoring and analysis of data, whether or not the patients participated in randomised trials.[25]

Cases

The present analysis includes all women, who had a completely resected invasive carcinoma of the breast and no signs of distant metastasis as determined by routine examinations (physical examination, clinical chemistry, chest radiography and other examinations if indicated). Cases with bilateral breast cancer were included (n=1535), and the tumour characteristics of the side with the least favourable prognostic impact were recorded in the DBCG registry. A negative sentinel node biopsy or axillary clearance (levels I and II) in combination with breast-conserving surgery or mastectomy was required. Radiotherapy to the breast was mandatory following lumpectomy. Further description of the database and treatment guidelines has been given elsewhere.[25 26]

From 1 June 1978 to 31 May 2010, 89 409 cases were registered. Of these, 3113 had a diagnosis of previous breast cancer, other malignancy (except non-melanoma skin tumours) or distant metastasis and 610 patients were not operated. Further excluded from the analyses were patients with unknown tumour size (n=2045) and/or unknown axillary lymph node status (n=5678). In total, 79 658 cases were included for further analyses (figure 1).

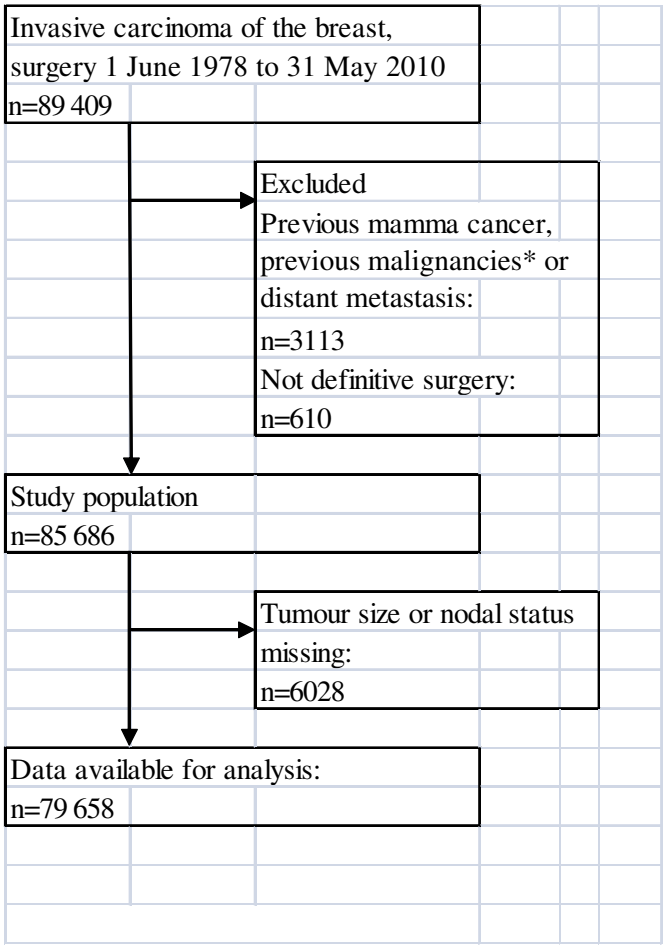

Figure 1 Flow diagram: prospective registration of Danish women operated for early breast cancer 1978–2010. *Except non-melanoma skin tumours.

Variables

The seasons of surgery, generally 1–3 weeks after the diagnosis, were defined as follows: winter (1 December to 28 or 29 February), spring (1 March to 31 May), summer (1 June to 31 August) and autumn (1 September to 30 November), so the summer period includes the months with the possibility of most sun exposure due to the altitude of the sun and vacations. Treatment periods were categorised according to the national programmes initiated in 1977, 1982, 1989, 1999, 2001, 2004 and 2007.[25] The age at surgery was categorised in intervals: ≤39, 40–49, 50–59, 60–69, 70–79 and ≥80 years. Tumour size was categorised according to the largest tumour diameter: 0–10, 11–20, 21–50 and ≥51 mm. The spread of breast cancer to locoregional lymph nodes was categorised as negative, one to three positive lymph nodes and four or more positive lymph nodes. The hormone receptor status was categorised as: negative, oestrogen receptor or progesterone receptor positive and unknown. The histopathological status was categorised in five groups as: grade I, II or III ductal carcinoma, lobular carcinoma and carcinoma of other types or unknown diagnosis. The frequency of allocated systemic treatment (chemotherapy and endocrine therapy) by season of surgery was reported.

End point

OS was measured from the date of surgery to the date of death. Observations were censored at emigration or at 1 June 2011, which was the date of data withdrawal of patient vital status from the Danish Centralised Civil Register.

Statistical analysis

The association between OS and season of surgery was analysed by Cox proportional hazards regression

models.[27 28] The effects of season of surgery were analysed in models with an increasing level of adjustment for prognostic variables: models stratified by treatment programme (adjusted I); models stratified by treatment programme and age at surgery (adjusted II) and models stratified by treatment programme, age at surgery, hormone receptor status and lymph node status and further including the effects of tumour size and histological type (fully adjusted). The interpretations of a seasonal effect on survival in these models differ according to the level of adjustment. In the fully adjusted model, the seasonal effect includes the effects of unknown or not included prognostic variables including the alleged effect of vitamin D. In the adjusted II model, the seasonal effect includes the effects of both known and unknown prognostic variables. In the adjusted I model, the seasonal effect further includes the effects of referral pattern, that is, patient age at

Table 1 Prognostic factors by season among 79 658 Danish women operated for early breast cancer between 1 June 1978 and 31 May 2010

	Winter		Spring		Summer		Autumn		Total	
Characteristic	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Total	18 760		20 067		20 033		20 798		79 658	
Age at surgery*										
≤39 years	1051	5.6	1057	5.3	1001	5.0	1094	5.3	4203	5.3
40–49 years	3249	17.3	3604	18.0	3524	17.6	3637	17.5	14 014	17.6
50–59 years	4906	26.2	5251	26.2	5232	26.1	5461	26.3	20 850	26.2
60–69 years	5203	27.7	5506	27.4	5520	27.6	5702	27.4	21 931	27.5
70–79 years	3233	17.2	3436	17.1	3541	17.7	3642	17.5	13 852	17.4
≥80 years	1118	6.0	1213	6.0	1215	6.1	1262	6.1	4808	6.0
Period of surgery†										
1977–1989	4592	24.5	4783	23.8	5115	25.5	5448	26.2	19 938	25.0
1990–1999	5626	30.0	6160	30.7	6359	31.7	6559	31.5	24 704	31.0
2000–2010	8542	45.5	9124	45.5	8559	42.7	8791	42.3	35 016	44.0
Tumour size‡										
0–10 mm	2832	15.1	3136	15.6	2972	14.8	3211	15.4	12 151	15.3
11–20 mm	7419	39.5	7983	39.8	7945	39.7	8310	40.0	31 657	39.7
21–50 mm	7469	39.8	7964	39.7	8053	40.2	8201	39.4	31 687	39.8
>50 mm	1040	5.5	984	4.9	1063	5.3	1076	5.2	4163	5.2
Nodal status§										
Negative	9767	52.1	10 672	53.2	10 723	53.5	11 233	54.0	42 395	53.2
1–3 positive	5772	30.8	5984	29.8	5915	29.5	6015	28.9	23 686	29.7
≥4 positive	3221	17.2	3411	17.0	3395	16.9	3550	17.1	13 577	17.0
Histological group¶										
Ductal grade I	4808	25.6	5129	25.6	5242	26.2	5390	25.9	20 569	25.8
Ductal grade II/?**	7268	38.7	7672	38.2	7542	37.6	7893	38.0	30 375	38.1
Ductal grade III	3351	17.9	3504	17.5	3517	17.6	3626	17.4	13 998	17.6
Lobular	1963	10.5	2135	10.6	2086	10.4	2137	10.3	8321	10.4
Other invasive	1370	7.3	1627	8.1	1646	8.2	1752	8.4	6395	8.0
ER–PgR status										
Negative	2919	15.6	3176	15.8	3299	16.5	3217	15.5	12 611	15.8
Positive	12 453	66.4	13 054	65.1	12 994	64.9	13 849	66.6	52 350	65.7
Unknown	3388	18.1	3837	19.1	3740	18.7	3732	17.9	14 697	18.5
Per cent Er–PgR positive†† ‡‡		81.0		80.4		79.8		81.1		80.6
Adjuvant systemic therapy										
None	9449	50.4	10 256	51.1	10 551	52.7	10 940	52.6	41 196	51.7
Chemotherapy§§	4749	25.3	5063	25.2	4849	24.2	5043	24.2	19 704	24.7
Endocrine therapy¶¶	6270	33.4	6629	33.0	6347	31.7	6654	32.0	25 900	32.5

*χ^2=12.2, df=15, p=0.66.
†χ^2=80.7, df=6, p=0.0001.
‡χ^2=14.9, df=9, p=0.09.
§χ^2=19.5, df=6, p=0.003.
¶χ^2=25.1, df=12, p=0.014.
**Unknown grade, n=1533.
††Positive relative to sum of positive and negative.
‡‡χ^2=12.7, df=3, p=0.005.
§§χ^2=11.7, df=3, p=0.009.
¶¶χ^2=18.4, df=3, p=0.0004.
ER, oestrogen receptor; PgR, progesterone receptors.

Table 2 Overall survival by Cox proportional hazards regression at survival periods 0–1, 0–2, 0–5 and 0–10 years post-surgery

Period of follow-up Season of surgery	Adjusted I* HR (95% CI)	 p Value	Adjusted II† HR (95% CI)	 p Value	Fully adjusted‡ HR (95% CI)	 p Value
0–1 years after surgery						
Winter	1 (reference)	0.053	1 (reference)	0.067	1 (reference)	0.052
Spring	1.07 (0.95 to 1.20)		1.06 (0.95 to 1.19)		1.07 (0.96 to 1.20)	
Summer	1.09 (0.97 to 1.22)		1.08 (0.96 to 1.21)		1.12 (1.00 to 1.25)	
Autumn	0.95 (0.84 to 1.06)		0.94 (0.84 to 1.06)		0.97 (0.86 to 1.09)	
0–2 years after surgery						
Winter	1 (reference)	0.19	1 (reference)	0.17	1 (reference)	0.43
Spring	0.99 (0.92 to 1.06)		0.98 (0.92 to 1.06)		1.00 (0.93 to 1.07)	
Summer	0.99 (0.92 to 1.06)		0.99 (0.92 to 1.06)		1.01 (0.94 to 1.08)	
Autumn	0.93 (0.87 to 1.00)		0.93 (0.86 to 1.00)		0.96 (0.89 to 1.03)	
0–5 years after surgery						
Winter	1 (reference)	0.60	1 (reference)	0.48	1 (reference)	0.96
Spring	0.98 (0.94 to 1.03)		0.98 (0.94 to 1.03)		1.00 (0.95 to 1.04)	
Summer	0.98 (0.94 to 1.02)		0.97 (0.93 to 1.02)		1.00 (0.95 to 1.04)	
Autumn	0.97 (0.93 to 1.01)		0.97 (0.93 to 1.01)		0.99 (0.95 to 1.03)	
0–10 years after surgery						
Winter	1 (reference)	0.90	1 (reference)	0.81	1 (reference)	0.92
Spring	1.00 (0.96 to 1.03)		1.00 (0.96 to 1.03)		1.01 (0.98 to 1.05)	
Summer	1.00 (0.96 to 1.03)		0.99 (0.96 to 1.03)		1.01 (0.98 to 1.05)	
Autumn	0.99 (0.95 to 1.02)		0.98 (0.95 to 1.02)		1.00 (0.97 to 1.04)	

Estimates of season of surgery are shown among 79 658 Danish women operated for breast cancer between 1 June 1978 and 31 May 2010.
*Model stratified for treatment programme.
†Model stratified for treatment programme and age at surgery.
‡Model stratified for treatment programme, age at surgery, hormone receptor status and nodal status and including the effects of tumour size and histological group.

surgery. The stratification of the Cox models was chosen to meet the proportional hazards assumption as assessed by Schoenfeld residuals plots.[27] The analyses were done for four survival periods: 0–1, 0–2, 0–5 and 0–10 years after surgery. The null hypothesis of no survival effect of season of surgery was assessed by the Wald χ^2 statistic, and a two-sided p value <0.05 was considered statistically significant. The HRs of season of surgery (winter as reference level) together with their 95% CIs are reported. Due to the long period of inclusion, the potential heterogeneity of seasonal effects according to period of inclusion was investigated in models including an interaction term of season of surgery and programme series (1977 and 1982 vs 1989 vs 1999, 2001, 2004 and 2007). Analysis was performed with SAS V.9.1 (SAS Institute).

RESULTS

The person-years of observation were 78 587 for the survival period 0–1 years, 151 980 for the survival period 0–2 years, 327 646 for the survival period 0–5 years and 516 011 for the survival period 0–10 years after surgery. For the latter group, the median observation period for patients without an event was 10.0 year. The basic characteristics of the patient material according to season of surgery are presented in table 1.

HRs of OS up to 10 years with surgery performed in winter as reference are given in table 2. Overall, no statistically significant association between OS and season of surgery are observed in 2-, 5- and 10-year follow-up periods. Only for the 1-year follow-up, a close to significant association is observed (p=0.052, fully adjusted analysis); OS is highest for patients undergoing surgery in autumn (HR: 0.97, 95% CI 0.86 to 1.09) and lowest for patients undergoing surgery in summer (HR: 1.12, 95% CI 1.00 to 1.26). Heterogeneity of seasonal effects according to period of inclusion was not statistical significant irrespective of model adjustment or survival period.

DISCUSSION

In the present study, we found no evidence of a seasonal variation in the OS among almost 80 000 Danish women with primary breast cancer. The strengths of this study are the sample size, the population-based approach in a limited geographic area,[29] the prospectively collected characteristics of tumour and lymph node status and the long follow-up (median 10.0 years). The detailed information's offer the possibility of including season of surgery in a multivariate analysis with the variables year, age at surgery, tumour size, nodal status, hormone receptor status and histopathological type. It should be noted that in our analysis, the 'adjusted II' models are stratified by treatment programme and age at surgery only. Thus, the estimates of association between OS and seasonal of surgery are not affected by the variables

potentially associated with vitamin D or season of surgery (tumour size, positive axillary nodes, high-grade tumours and oestrogen receptor/progesterone receptor status). Using this approach, the independent prognostic effect of season of surgery seems to disappear. The limitations of the study are the lack of information about serum vitamin D in the individual patient at the time of surgery. Using the estimated UV dose as surrogate for vitamin D status must cause reservation, as it is not known whether vitamin D status of the breast cancer patients follow that of the background population. Lack of seasonal variation in this study does not necessarily mean that vitamin D is not important for the OS for breast cancer patients. The serum vitamin D in Danish women treated for breast cancer could be so low even among patients treated in the summer–autumn so that no difference could be detected. One nested case–control study (N=142) showed lower serum vitamin D among Danish patients at the diagnostic mammography.[14] Cross-sectional studies of the plasma vitamin D in healthy Danish volunteers demonstrate a higher level in summer–autumn than in winter–spring.[24]

Results from UK and Norway indicate a better prognosis if diagnosis of breast cancer takes place during the summer or autumn.[20–22] This seasonal variation was interpreted as a result of vitamin D deficiency in the dark months of the year, although one author considered the possibility that the seasonal effect might be due to a relative higher rate of diagnoses in summer and the prevalence of infections during wintertime leading to early death.[20] In contrast, results from Sweden demonstrate a worse OS for patients diagnosed in the summer probably due to a relative reduction in the number of early stage diagnoses from mammography screening which are closed in the summer months and the healthcare system treating primarily the most sick patients in holiday periods.[23 30] Breast cancer is regarded as a relatively slow growing cancer, with a long preclinical course.[31] If vitamin D level should be of etiologic or prognostic importance, it is supposed that the influence is working over a longer time period and not just reflected by vitamin D status at time of diagnosis. If the level of vitamin D at the time of surgery should influence prognosis, the mechanism must be differences in perioperative resistance to cancer dissemination and the logical precaution would be to ensure a high preoperative vitamin D level. However, limited evidence including the present study supports this statement.

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Competing interests All authors have completed the ICMJE disclosure form (available on request from the corresponding author) and declare: no support from any organisation for the submitted work, no financial relationships with any organisations that might have an interest in the submitted work in the previous 3 years and no other relationships or activities that could appear to have influenced the submitted work.

Ethics approval The data are from Danish Breast Cancer Group.

Contributors DT contributed to conception and interpretation of data, reviewed the literature, drafted the article and finally approved the submitted paper. KDB analysed and interpreted the data, drafted the statistical part and finally approved the submitted paper. AMT and NK contributed to the interpretation of data, revised it critically for important intellectual contents and finally approved the submitted paper.

Provenance and peer review Not commissioned; externally peer reviewed.

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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort study* *BMJopen-2011-000358*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	2
Objectives	3	State specific objectives, including any prespecified hypotheses	2-3
Methods			
Study design	4	Present key elements of study design early in the paper	3
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	3
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	3-4
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	3-4
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	4-5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	4
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	5
		(*b*) Describe any methods used to examine subgroups and interactions	5
		(*c*) Explain how missing data were addressed	
		(*d*) If applicable, explain how loss to follow-up was addressed	
		(*e*) Describe any sensitivity analyses	5-6
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6 + fig. 1
		(b) Give reasons for non-participation at each stage	fig.1
		(c) Consider use of a flow diagram	fig.1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1
		(b) Indicate number of participants with missing data for each variable of interest	4 + fig. 1
		(c) Summarise follow-up time (eg, average and total amount)	6
Outcome data	15*	Report numbers of outcome events or summary measures over time	Table 2
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	6 + table 2
		(*b*) Report category boundaries when continuous variables were categorized	4 + table 2
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	6-7
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	7
Generalisability	21	Discuss the generalisability (external validity) of the study results	7
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	No funding

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.