Bereavement care in general practice: a cluster-randomized clinical trial

Mai-Britt Guldin¹,*, Peter Vedsted¹, Anders Bonde Jensen¹, Frede Olesen¹ and Robert Zachariae³

¹Research Unit for General Practice, University of Aarhus, ²Department of Oncology, Aarhus University Hospital and ³Research Unit for Psycho-Oncology, University of Aarhus, Aarhus, Denmark.
*Correspondence to Mai-Britt Guldin, Research Unit for General Practice, University of Aarhus, Bartholins Allé 2, 8000 Aarhus C, Denmark; E-mail: m.guldin@alm.au.dk

Received 28 March 2012; Revised 31 July 2012; Accepted 8 August 2012.

Background. The loss of a loved person may lead to complicated grief (CG). General practitioners (GPs) consider bereavement care to be important but find training for this task to be insufficient. We hypothesized that improvement in skills that facilitate early identification of CG and enhance GPs’ clinical care may reduce adverse health outcomes.

Aim. To test whether implementation of a bereavement management program in general practice could improve the GPs’ ability to identify CG and provide clinical care.

Design. A cluster-randomized controlled trial allocating GPs and their listed patients suffering from bereavement to either a intervention or a control group.

Setting. Close relatives of patients who had died from cancer in Denmark were recruited (N = 402).

Method. The primary outcomes were defined as the bereaved relatives’ score on the Beck’s Depression Inventory II and the Inventory of Complicated Grief-Revised (ICG-R), the GP’s clinical assessment of the relative’s grief reaction and the relative’s number of contacts with general practice.

Results. Larger improvements in ICG-R scores were found in the intervention group than in the control group. In the intervention group, patients exhibiting CG symptoms were more likely to receive supportive care and to be referred to mental health practitioners, whereas GP’s in the control group more often prescribed psychotropic drugs for patients with symptoms of CG. The GP’s ability to identify CG at 13 months did not seem to be better in the intervention group than in the control group.

Conclusion. While only statistically near significant, we found some indications of an effect of the intervention compared with usual care. Our results underscore the need for improving GPs’ clinical skills in identifying patients with CG.

Keywords. Death and dying, palliative care/end-of-life care, psychotherapy/counselling, public health, risk assessment.

Introduction

In some persons, bereavement is accompanied by impaired health.¹ Bereavement-related psychological problems, often termed ‘complicated grief’ (CG), include insufficient adjustment to the loss, high levels of distress, and avoidant behaviours.²,³ It is estimated that in 7–15% of all bereaved persons will suffer from CG. CG is associated with long-term psychological dysfunction, considerable impairment of social and occupational functioning, increased medication and negative consequences on physical health in about 7–15% of all bereaved persons.²,⁴ Recent studies have shown that cancer patients’ relatives are facing a special risk of CG following their loss, which has been ascribed to the extensive period of exhausting care giving preceding their loss.⁵

A recent meta-analysis found that psychotherapeutic interventions to help bereaved persons generally had limited effects, except interventions for CG which were found to have effects comparable with those of psychotherapy for other disorders.⁶ A main clinical challenge is to distinguish coping processes that facilitate adjustment to loss from those that do not.⁷,⁸ The dual-process model of adaptive coping describes the process of adjustment to loss.⁹,¹⁰ This model
assumes that grief is facilitated by a balanced dosage of emotional coping and restoring of everyday life without the person who has been lost. Facilitating this coping process is considered a valuable part of treatment.

In the Danish healthcare system, the general practitioner (GP) acts as the medical frontline professional meeting bereaved relatives, and the GP acts as a gatekeeper with regard to referrals to specialist services. A systematic literature review of bereavement care in primary care showed that many GPs viewed bereavement care as an ‘important and satisfying part of their work for which they had received little training’. Skills improvement that facilitates GPs’ early identification of CG and enhances their clinical care may optimize treatment planning and improve bereaved relatives’ health outcomes. We, therefore, investigated whether a heightened awareness of bereavement among GPs and improved skills in stratifying patients into groups with high and low need for help improved their ability to identify CG and to provide appropriate care. The aim of the present study was to test whether dissemination of information about bereavement and risk factors for CG to GPs would (i) improve detection of CG, (ii) ensure that more CG patients receive proper treatment and (iii) alleviate grief symptoms more efficiently than usual care.

Methods

Setting
The Danish healthcare system is tax financed and medical care is free. Almost all Danish citizens (98%) are listed with a general practice, and the GP plays a coordinating role in health care. Furthermore, GPs cooperate to supply out-of-hours medical services during weekdays 4 p.m. to 8 a.m., on weekends and bank holidays. All Danish citizens are assigned a unique central person registration number at birth, which makes it possible to link all health registers with a specific person and provider.

Study design
The study was a cluster-randomized controlled trial (RCT) with two parallel groups of GPs and their listed bereaved relatives of deceased cancer patients. The reporting of the trial adheres to the CONSORT statement recommendations.

Participants
Newly bereaved persons were recruited consecutively when a cancer patient had died at one of the inclusion facilities at Aarhus University Hospital or Bispebjerg Hospital, Copenhagen University Hospital, Hospice Söholm or Hospice Djursland. Inclusion criteria were the following: >17 years, registration with a Danish GP and informed consent. Exclusion criteria were poor Danish language skills or cognitive impairment, which would hinder questionnaire response. The inclusion period went from 11 June 2009 to 31 December 2010, and a total of 745 relatives were assessed for eligibility. The flow of participants is shown in Figure 1. Inclusion facilities collected data on eligible participants, and the main reason for declining participation (=non-participation) was ‘no need for a bereavement intervention’.

Of the eligible 317 GPs, 314 (99%) returned a questionnaire, representing 158 different general practices. Of these, 230 (73%) reported having contact with the relative during the 13 months following the loss, and 160 (70%) reported having communicated with the relative about the bereavement process.

Intervention
The intervention consisted of information pamphlets to both GPs and patients, which were sent by mail after completion of the baseline questionnaire. The pilot-tested pamphlets featured updated information on CG symptoms, the dual-process model of adaptive coping and risk factors for the development of CG. GPs were also informed about the results of the patient’s baseline risk assessment based on the depression level 8 weeks post-loss. Lastly, GPs received information on how to assess CG and simple suggestions on how to support the patient, for instance, to ask about which reactions to grief the patient was experiencing and relate the reactions to the dual-process model of adaptive coping. Patients were encouraged to contact their GP if they showed signs of depression or CG or worried about their bereavement reaction.

Measures
Questionnaires were mailed to the bereaved participants 2, 6 and 13 months post-loss. If the bereaved participant was still in the study 13 months after the loss, a clinical assessment questionnaire was sent to the GP.

The assessment battery for the bereaved participants consisted of Beck’s Depression Inventory II (BDI-II) and the Inventory of Complicated Grief-Revised (ICG-R) and socio-demographic questions.

BDI-II
The BDI-II is a 21-item scale widely used to assess symptoms of depression. Statements are rated by the respondent (range 0–3) according to the intensity of the symptom experienced during the past 2 weeks. For ethical reasons, item 21, which addresses sexuality, was provided with an additional response option at baseline: ‘does not apply’, which was scored 0. This was done as pilot testing showed that the question was considered offensive by respondents who had suffered a spousal loss. At follow-ups, the response categories were restored to the usual version. Scores were calculated as means and according to the manual to indicate a symptom level suggestive of depression: scores 14–19 denominates mild depression, 20–28 moderate depression and 29–63 severe depression. For the early risk assessment, a BDI
score > 19 was considered a risk factor for developing CG, as this level had predicted risk of complications in cancer patients' relatives in a previous study.15

ICG-R
CG was measured with the ICG-R, which is a modified version of the Inventory of Complicated Grief by Prigerson and colleagues.17 The ICG-R has previously been shown to have a high internal consistency (Cronbach’s α > 0.94) and a 6-month test–retest reliability of 0.80.17 The sum scale is based on 15 items with a five-point Likert-scale response format (sum score range of 15–75), a functional criterion and a duration criterion of 6 months.17 Thus, the first assessment of CG was 6 months post-loss. Scores were calculated as a sum score of all items, as well as dichotomized scores. When using the dichotomized scores, the suggestions of the authors of the scale were followed, and a cut-off of 25 was used to indicate a symptom level suggestive of CG.17

Clinical grief assessment by the GP
The GP made the clinical grief assessment 13 months post-loss based on a piloted ad hoc form. Clinical risk was measured with the question: ‘How would you characterize this patient’s grief reaction’. Response options were the following: ‘Unproblematic’, ‘At risk’, ‘Complicated reaction’ and ‘Insufficient knowledge about the grief reaction’. The GP was also asked which treatment options (s)he had used to manage the patient’s grief reaction.

Figure 1 Flow chart of the cluster-randomized trial. Participants were sampled as the relatives to deceased cancer patients who had died at specific departments, hospices or while receiving palliative care.
Registry-based data on contacts to the GP
Data on primary care services used were obtained from the Danish National Health Service Register, which monitors activities in the primary health care system.\textsuperscript{18} Contacts with general practice during the daytime were defined as face-to-face contacts, telephone consultations, home visits and conversational therapy sessions per month. Out-of-hours contacts were defined as the sum of telephone consultations, consultations and home visits per month.

Randomization
Cluster randomization was performed at practice level. Each Danish general practice has a unique identification number, so GPs working in group practices were randomized together. At the outset of the study, all Danish general practices were allocated either to the intervention group or to the control group by a computerized random number generator with an unpredictable allocation sequence. When a bereaved was included, s(he) was automatically allocated to the group of his or her GP. Allocation status was blinded to the researcher but became evident to the bereaved participants and their GPs as information pamphlets were sent to the participants in the intervention group as part of the intervention.

Statistical analyses
Sample size was calculated on the basis of an estimate that 20% of deceased cancer patients’ bereaved relatives would experience CG and that 50% of patients with psychiatric problems are diagnosed in general practice. We set the minimal relevant difference in detection rates to 10% with alpha = 5% and beta = 80% and while considering the design effects of cluster randomization (correction factor 1.5) and dropout rates, the total number needed to include was set to 600 bereaved patients.

Participant responses at baseline and at the 6- and 13-month follow-up were analyzed together with the responses on the GP questionnaires according to intention to treat. Non-responder analyses were conducted based on the data on non-participants to assess potential selection bias. The prevalence of symptoms suggestive of depression and CG was calculated at 2 (BDI only), 6 and 13 months based on mean scores and dichotomized scores according to recommended cut-offs for the scales. The differences in sum scores between the groups were tested with a Mann–Whitney rank sum test.

The sensitivity and the specificity of the GPs’ clinical assessment of the bereavement reaction were analyzed with the dichotomized answers of the BDI and ICG-R as the golden standard. The risk and risk differences of receiving designated treatment options were analyzed based on the symptom level of CG at 6 months to test whether CG at baseline yielded different treatments in the groups.

Confidence intervals (CIs; 95%) for incidence rates (IRs) of GP contacts before and after loss and for corresponding rate ratios (IRR) between groups were assessed using a negative binomial model.\textsuperscript{19} Robust variance estimation with practice as the unit of clustering was applied to account for the dependence structure at GP and practice level. Proportions of patients experiencing at least one contact in each period were analyzed similarly in a generalized linear binomial model using logarithmic link function accommodating estimation of relative risks.

Statistical significance was set to 0.05 or less. All analyses were conducted with Stata version 11.1.

Ethics
The project was approved by the Regional Science Ethics Committee (J.nr. 2008-02-25), and the Danish Data Protection Agency approved the research database (J.nr. 2009-41-2992). The RCT was indexed at www.clinicaltrials.gov (ID number: NCT01292512).

Results
Participant characteristics
Non-participating relatives differed from participating with respect to gender (31% of the women and 43% of the men declined, $P = 0.002$) and their relation to the deceased ($P < 0.001$).

Participant characteristics are shown in Table 1. The two randomized groups were well balanced with no statistically significant differences between the intervention group and the control group concerning the characteristics shown in Table 1.

Prevalence of depression and CG
The prevalence of symptoms suggestive of depression and CG in the two groups is shown in Table 2. In the intervention group, the number of patients with symptoms suggestive of CG decreased from 38 (22%) at 6 months post-loss to 24 (15%) at 13 months post-loss, and from 29 (19%) at 6 months to 25 (18%) at 13 months post-loss in the control group. The changes in sum score between the two groups did not reach statistical significance ($P = 0.07$; Mann–Whitney test).

Clinical grief assessment and treatment options in general practice
Clinical grief assessment was performed by the GPs for 155 (53%) relatives at 13 months post-loss. In the intervention group, 26 (15%) of the relatives were assessed to suffer from a level of bereavement-related distress that required treatment, and 9 (35%) had a true abnormal diagnosis; the corresponding number in the control group was 16 (11%) and 8 (50%), respectively. The sensitivity of the GP’s assessment in the intervention group was 42.9%
<table>
<thead>
<tr>
<th></th>
<th>Control group</th>
<th>Intervention group</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean age (range)</strong></td>
<td>50.0 (18; 83)</td>
<td>51.8 (20; 87)</td>
<td>0.21</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>135 (72)</td>
<td>151 (70)</td>
<td>0.67</td>
</tr>
<tr>
<td>Male</td>
<td>52 (28)</td>
<td>64 (30)</td>
<td></td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Widowed</td>
<td>69 (38)</td>
<td>79 (37)</td>
<td>0.21</td>
</tr>
<tr>
<td>Married/partnership</td>
<td>83 (45)</td>
<td>104 (49)</td>
<td></td>
</tr>
<tr>
<td>Never married</td>
<td>9 (5)</td>
<td>7 (3)</td>
<td></td>
</tr>
<tr>
<td>Separated/divorced</td>
<td>18 (10)</td>
<td>19 (9)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>5 (3)</td>
<td>4 (2)</td>
<td></td>
</tr>
<tr>
<td>Relationship of deceased</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spouse/partner</td>
<td>69 (38)</td>
<td>83 (40)</td>
<td>0.57</td>
</tr>
<tr>
<td>Parent</td>
<td>74 (40)</td>
<td>87 (41)</td>
<td></td>
</tr>
<tr>
<td>Child</td>
<td>9 (5)</td>
<td>14 (7)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>31 (17)</td>
<td>26 (12)</td>
<td></td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤10 years of education</td>
<td>82 (45)</td>
<td>100 (48)</td>
<td>0.66</td>
</tr>
<tr>
<td>&gt;10 ≤15 years of education</td>
<td>75 (41)</td>
<td>78 (37)</td>
<td></td>
</tr>
<tr>
<td>&gt;15 years of education</td>
<td>24 (13)</td>
<td>32 (15)</td>
<td></td>
</tr>
</tbody>
</table>

*Figures in () are percent (%) unless otherwise noted.
*T-test or Chi² test used to test differences between groups.

Table 2: Mean scores and prevalence of symptom level suggestive of depression and CG in the intervention and control group at baseline and follow-ups

<table>
<thead>
<tr>
<th></th>
<th>Intervention/Control</th>
<th>Grief symptoms* Intervention/Control</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cut-off score</td>
<td>Mild depression 32 (16%)/38 (21%)</td>
<td>Moderate depression 28 (14%)/17 (9%)/Severe depression 6 (3%)/12 (7%)</td>
</tr>
<tr>
<td>6 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean score</td>
<td>9.23 [7.95–10.52]/10.19 [8.69–11.68]</td>
<td>17.18 [15.45–18.92]/17.06 [15.35–18.78]</td>
</tr>
<tr>
<td>Cut-off score</td>
<td>Mild depression 24 (13%)/21 (14%)</td>
<td>Moderate depression 12 (7%)/14 (9%)/Severe depression 8 (4%)/8 (5%)/Complicated grief 38 (22%)/29 (19%)</td>
</tr>
<tr>
<td>13 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cut-off score</td>
<td>Mild depression 19 (11%)/18 (13%)</td>
<td>Moderate depression 10 (6%)/10 (7%)/Severe depression 5 (3%)/6 (4%)/Complicated grief 24 (15%)/25 (18%)</td>
</tr>
</tbody>
</table>

[95% CI: 21.8–66.0] and the specificity 73.8% (95% CI: 61.5–84.0); the positive predictive value was 34.6% (95% CI: 17.2–55.7) and the negative predictive value 80% (95% CI: 67.7–89.2). In the control group, sensitivity was 40% (95% CI: 19.1–63.9), specificity 83.7% (95% CI: 70.3–92.7), the positive predictive value 50% (95% CI: 24.7–75.3) and the negative predictive value 77.4% (95% CI: 63.8–87.7). Table 3 shows the likelihood of receiving a range of treatment options in general practice in relation to having CG or not.

*Measured at 6 and 13 months post-loss.

Contact rates in general practice

Contact frequencies with GPs were generally higher in the control group both before and after the loss (see Fig. 2). Compared with the control group, IRs were lower among bereaved relatives in the intervention group after the loss [IR = 4.68 (95% CI = 3.90–5.62)/5.08 (95% CI = 4.33–5.96); IRR = 0.92 (95% CI = 0.72–1.17); P = 0.50]. For out-of-hour contact, the difference in IRs was more evident [IR = 0.08 (95% CI = 0.05–0.13)/0.15 (95% CI = 0.09–0.25); IRR = 0.55 (95% CI = 0.29–1.06); P = 0.07].
Table 3  The likelihood of receiving a designated treatment in general practice in the intervention group and the control group in relation to having symptoms suggestive of CG or not

<table>
<thead>
<tr>
<th></th>
<th>Intervention group</th>
<th>Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Risk</td>
</tr>
<tr>
<td>CG/not CG Information</td>
<td></td>
<td></td>
</tr>
<tr>
<td>About help seeking, group counselling, etc.</td>
<td>9/20</td>
<td>23.7/14.4</td>
</tr>
<tr>
<td>Supportive care</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Support and counselling about grief reactions</td>
<td>14/31</td>
<td>36.8/22.3</td>
</tr>
<tr>
<td>Diagnostic consideration</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression, PTSD or other Referral</td>
<td>8/18</td>
<td>21.1/12.9</td>
</tr>
<tr>
<td>To a mental health professional</td>
<td>11/18</td>
<td>28.9/12.9</td>
</tr>
<tr>
<td>Medicine prescription</td>
<td></td>
<td></td>
</tr>
<tr>
<td>For a psychotropic drug</td>
<td>8/13</td>
<td>21.1/9.4</td>
</tr>
</tbody>
</table>

Proportions are shown in actual numbers, risk and risk ratio with 95% CI and P values.

Figure 2  Contacts with the GP during daytime and out-of-hours services 6 months prior to the loss and 6 months post-loss. The graphs show incidence rates (mean number of contacts) for the intervention and control group and proportion in each group receiving at least one service with a 95% CI. Corresponding incidence rate ratios and risk ratios between groups are presented and adjusted for relative risk based on number of contacts prior to loss.
Discussion

Main findings
In this RCT of an information-oriented intervention targeted at GPs and bereaved patients with a symptom level suggestive of CG, the data suggested that more participants in the intervention group than in the control group improved from 6 to 13 months post-loss. Participants in the intervention group did not differ from controls with respect to contacts with their GPs, and their consumption of out-of-hours services fell slightly. GPs in the intervention group more often chose to give information, supportive care and referrals to a mental health practitioner, whereas GPs in the control group favoured prescription of psychotropic medicine. While none of the observed improvements reached statistical significance, the results could be interpreted as sufficiently encouraging to suggest further studies of GPs’ bereavement care. We found low CG and depression identification rates in both groups, and GPs in the intervention group in particular had problems diagnosing bereavement-related mental health conditions. This finding testifies to the need for enhancing skills-oriented training in GP’s pre- and postgraduate training within this area.

Comparison with existing literature
To our knowledge, no previous trial has tested the effect of a structured information strategy targeting CG and supportive care for bereaved patients in general practice. In the meta-analysis by Wittouck and colleagues, psychotherapy to patients with CG was efficacious; although effect sizes immediately after treatment were small, the difference in CG increased over time. Even though the present intervention was not psychotherapy, it could be speculated whether differences in CG scores would increase over time and yield a more convincing result.

Strengths and limitations
The results of the present study may be affected by some of the study’s limitations. A larger sample size with increased statistical power would have added more precision to the estimates, and the absence of effect could potentially be due to a type 2 error as sample size ended up smaller than anticipated by power calculation estimates. The recruitment procedure also carries a risk of systematic bias as we cannot be sure that the included participants were representative of the population at large. On the other hand, we expect differences are equally distributed between the two groups due to the randomization procedure wherefore any selection bias would have no effect on the comparison between the groups. Men were under-represented in the study, as were relatives with a relation to the deceased other than spouse or child. This possibly limits the generalization of the results to these groups of bereaved relatives.

The lack of an authorized and validated diagnosis and measure of pathological grief reactions remains a methodological weakness in the present study like in all similar studies. We used CG as a measure of bereavement-related distress, and while the ICG-R is a widely used scale for measuring CG, a Danish validation is not available. We defined a cut-off according to the instructions of the authors of the ICG-R, and the results are, therefore, comparable to those reported in other studies of CG.

A further point of discussion is the magnitude of the effect of the chosen intervention. The intervention was to provide information about assessment of CG and supportive care for bereaved individuals. This intervention could readily be implemented if shown successful, however, a limitation of such a design is that it reduces the opportunities to undertake a detailed evaluation of the adherence to and effectiveness of the individual components of the information packets. The sensitivity and the positive predictive value of identifying CG were very low. The GPs’ ability to assess mental health problems is important to efficient health care utilization and optimization of targeted support. The identification rates may be low for several reasons. First, the ICG-R has not been validated in Danish population, which might have influenced the accuracy of the cut-off. We did undertake a pilot test, which indicated that the questions were comprehensible to the GPs. Second, lack of knowledge about predictors and symptoms of complications during bereavement made it difficult for health professionals to undertake the clinical assessment. It should be noted that the sensitivity was equally low for depression, which is an established diagnosis. Third, not all GPs consider bereavement to represent a therapeutic challenge in general practice. Finally, it is possible that at least some bereaved patients refrained from telling their GP how much emotional distress they were experiencing, especially if they were not asked directly.

The randomization procedure appeared to be successful with no differences between groups. Yet, when register data were analyzed, a surprising difference in the contact rate emerged. Still, there was no difference in proportion of patients seeking contact in the two groups, and we estimated that this was not a flaw in the randomization procedure. The difference in contact rates was taken into account in the data analysis by adjusting the calculation of contact rates for differences pre-loss. Analyses on longer follow-up times should be made to establish long-term effects.

Another key issue is whether the intervention can be applied to other populations and in different settings. This bereavement intervention was targeted at general
practice for deceased cancer patients’ relatives. Further research is needed to shed light on the question of generalizability, especially to sudden and unexpected losses and in settings outside primary care.

Conclusion
To the best of our knowledge, this is the first RCT of bereavement care in general practice. We found some, albeit only statistically near significant, indications of an effect of active bereavement intervention targeted at patients and their GPs. The results underpin the need for more research to validate our findings in larger samples, to test potential moderators of treatment response and to improve the identification and treatment of CG in primary care. The difficulties in identifying those in greatest need for help stress the need for a standardized instrument for assessing CG in a clinical setting and for the development of clinical guidelines on assessment and support in the context of bereavement-related distress.

Acknowledgements
The authors wish to thank all the bereaved relatives and health care professionals who participated in this study: Palliative Care Team, Randers; Palliative Care Team, Silkeborg; Palliative Care Team, Aarhus; Hospice Søholm; Hospice Djursland; Department of Oncology, Department of Haematology and Department of Urology at Aarhus University Hospital; and the Department of Palliative Care at Bispebjerg Hospital, Copenhagen University Hospital. We also wish to thank IT manager Hanne Beyer for setting up the research databases and IT manager Kaare Rud Flarup for his help with register data. We also acknowledge statistician Morten Fenger-Gron for helpful data analysis.

Declaration
Funding: Danish Cancer Society (KP08005), the TrygFonden (J nr 7-09-0126), the Daehnfeldt Foundation and the Quality and Continuing Training Council for GPs in the Central Region Denmark. Ethical approval: Regional Science Ethics Committee (J.nr M-20080225), and the Danish Data Protection Agency approved the research database (J.nr. 2009-41-2992). The RCT was indexed at www.clinicaltrials.gov (ID number: NCT01292512).

Conflict of interest: none.

References