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SEASONAL FAYRE

Frankincense: systematic review

E Ernst

Abstract

Objective To assess evidence from randomised clinical trials about the effectiveness of extracts of *Boswellia serrata* (frankincense).

Design Systematic review.

Data sources Electronic searches on Medline, Embase, Cinahl, Amed, and Cochrane Library. Hand searches of conference proceedings, bibliographies, and departmental files.

Review methods All randomised clinical trials of *B serrata* extract as a treatment for any human medical condition were included and studies of *B serrata* preparations combined with other ingredients were excluded. Titles and abstracts of all retrieved articles were read and hard copies of all relevant articles were obtained. Selection of studies, data extraction and validation were done by the author. The Jadad score was used to evaluate the methodological quality of all included trials.

Results Of 47 potentially relevant studies, seven met all inclusion criteria (five placebo controlled, two with active controls). The included trials related to asthma, rheumatoid arthritis, Crohn's disease, osteoarthritis, and collagenous colitis. Results of all trials indicated that *B serrata* extracts were clinically effective. Three studies were of good methodological quality. No serious safety issues were noted. **Conclusions** The evidence for the effectiveness of *B serrata* extracts extracts is encouraging but not compelling.



BAL/GETTY IMAGES

Frankincense: an early non-steroidal anti-inflammatory drug? Frederich Overbeck: *The Adoration of the Kings* (1813), Kunsthalle, Hamburg

Introduction

When they saw the star, they rejoiced exceedingly with great joy. And going into the house they saw the child with Mary his mother, and they fell down and worshiped him. Then, opening their treasures, they offered him gifts, gold and frankincense and myrrh. (Matthew 2, 10-11, English Standard Version)

Frankincense, also known as olibanum, is the resin from the trees of the genus *Boswellia*, native to Arabia and India. It has a long history of use—for example, in religious ceremonies and for perfume production—and its medicinal properties have been appreciated for millennia.¹ Recently, the pharmacological properties and clinical effectiveness of *Boswellia serrata* have been studied systematically.

The aim of this systematic review was to summarise and critically evaluate the evidence from all randomised clinical trials of *B serrata* extracts.

Methods

Searches were done of Amed, Cinahl, Embase, and Medline databases (on 18 August 2008, each from its inception, using the Ovid Sp Interface), the Cochrane Library, and our departmental files, including conference proceedings. Four search terms (Boswellia.mp, Boswelli/ mesch, "Boswellia serrata".mp, Frankincense.mp) were constructed using a combination of MeSH and free-word terms on the individual databases. Results were initially screened by title to exclude any obviously irrelevant articles, and potential hits were downloaded into Endnotes files. No language restrictions were applied.

Clinical trials had to be randomised, include human patients with any medical condition, and use *B serrata* extracts as a monopreparation. Studies of preparations containing *B serrata* in combination with other ingredients,^{2 3} non-randomised trials,^{4 5} and abstracts reporting incomplete data for evaluation were excluded.

Data were extracted and validated in accord with predefined criteria (table). Two independent reviews assessed methodological quality with the Jadad score.⁶ A meta-analysis was not possible because of heterogeneity, so results are presented in narrative form.

Results

Seven randomised clinical trials were included (fig 1).⁷⁻¹³ The table summarises key data. The studies were published between 1998 and 2008 and most came from India. Methodological quality was variable but three trials reached the maximum on the Jadad scale.^{10 11} ¹³ Five trials were placebo controlled and two were

Key data from randomised clinical trials included in systematic review

First author (year), country	Condition (sample size)	Design (Jadad score)*	Interventions	Primary outcome measure	Main results/effect size‡	Adverse effects of BSE (A) and control intervention (B)	Comment
Gupta (1998), India/Germany ⁷	Asthma (80)	DB, PC, 2 PG (3)	(A) BSE (350 mg 3×day) for 6 weeks; (B) placebo	Percentage of patients showing clinical improvement	(A) 70% remission; (B) 27% remission§	(A) 2 patients experienced stomach pain, hyperacidity, nausea; (B) no information	Group (A) had more severe asthma than group (B); other endpoints also suggested efficacy of BSE
Sander (1998), Germany ⁸	Rheumatoid arthritis (37)	DB PC, 2 PG (2)	A) BSE (3600 mg 9×day) for 12 weeks; (B) placebo; both groups also received conventional drugs	Ritchie Index	Non-significant trend in favour of BSE§	(A) Stomatitis (1 patient); (B) eczema (1 patient), nausea (1 patient), increase of joint pain (1 patient)	Report only relates to subset of patients from larger unpublished study
Gerhardt (2001), Germany/Austria ⁹	Crohn's disease (102)	DB, 2PG, non- inferiority (3)	(A) BSE (3.6 g per day) for 8 weeks; (B) mesalazine (4.5 per day)	Crohn's Activity Index (CAI)	Non-inferiority of BSE confirmed: (A) CAI from 301 (63) to 192 (114); (B) from 282 (72) to 163 (96)	(A) No causally related adverse effects; (B) 13 causally related adverse effects	Data refer to intention to treat analysis
Kimmatkar (2003), India ¹⁰	Osteoarthritis of the knee (30)	DB, PC, crossover (5)	(A) BSE (333 mg per day) for 8 weeks; (B) placebo	Pain, function (VAS)	Significant intergroups differences in favour of BSE; intergroup difference for pain 2.3 (0.61)	(A) Diarrhoea (1 patient), epigastric pain, nausea (1 patient);(B) no information	Authors state that the differences are clinically relevant
Madisch (2007), Germany ¹¹	Collagenous colitis (31)	RCT, DB, PC, 2 PG (5)	(A) BSE (400 mg 3×day) for 6 weeks; (B) placebo	Percentage of patients with remission	(A) 64% remission (95% Cl 30.8 to 89.1, ITT 44%); (B) 27% (7.7 to 55.1, 27%)	(A) Dizziness, hypoglycaemia, lack of appetite, diarrhoea (1 patient), bacterial enteritis (1 patient); (B) no information	Other outcome measures (such as stool frequency) also suggest efficacy of BSE
Sontakke (2007), India ¹²	Osteoarthritis of the knee (66)	RCT, open, active control, 2PG (2)	(A) BSE (333 mg 3×day) for 6 months; (B) valdecoxib (10 mg, 1×day)¶	WOMAC scale	Pain: (A) from 245.3 (77.6) to 82.9 (62.3) at 6 months; (B) from 246.0 (71.4) to 85.4 (68.9)	(A) Diarrhoea (1 patient); (B) no adverse effects	1 month after discontinuation of therapy, patients in group (A) maintained benefit while those in (B) deteriorated
Sengupta (2008), India ¹³	Osteoarthritis of the knee (75)	RCT, DB, PC, 3 PG (5)	(A) BSE (100 mg per day) for 90 days, (B) BSE (250 mg per day), (C) placebo	Pain (VAS), Lequesne Index, WOMAC Index	Significant inter-group differences in favour of (A) and (B) versus (C); pain: (A) from 57.1 (8.7) to 21.4 (7.1); (B) from 55.6 (9.3) to 14.2 (6.8); (C) from 55.9 (12.0) to 41.8 (16.0)	Diarrhoea, nausea, abdominal pain, fever, weakness; evenly distributed between groups	Other outcome measures also suggest efficacy of BSE

BA=boswellic acid; BSE=Boswellia serrata extract; CRP=C-reactive protein; DB=double blind; ESR=erythrocyte sedimentation rate; MC=multicentre; PC=placebo controlled; PG=parallel groups; VAS=visual analogue scale; WOMAC=Western Ontario and McMasters Universities Osteoarthritis Index.

*Studies were superiority trials unless otherwise stated

‡Values are mean (SD) unless otherwise indicated; values in parentheses not identified in Sontakke study.

§No further information provided.

¶Trial done before withdrawal of valdecoxib from market.

comparisons against active treatments. All studies used oral administration of *B serrata* extracts.

Boswellia extracts showed some promise in treating asthma,⁷ rheumatoid arthritis,⁸ Crohn's disease,⁹ knee osteoarthritis,¹⁰ ¹² ¹³ and collagenous colitis.¹¹ However, all the included trials had flaws: the most common limitations were small sample size and incomplete reporting of data. The largest study included 102 patients, which



Flow chart showing study selection

is not large considering that this was a non-superiority trial.⁹ Crucially, little independent replication was found; for only one of the five different indications (osteoarthritis) had more than one randomised clinical trial been published.¹⁰ ¹² ¹³

Adverse effects of *B serrata* were minor and were judged as not causally related to the treatment and not markedly different from those noted in the placebo groups (table). Diarrhoea, abdominal pain, and nausea were reported in more than one study.

Discussion

Collectively, these data seem to indicate that *B* serrata extracts are effective in treating a range of conditions caused or maintained by inflammatory processes. The results of non-randomised studies and trials of herbal mixtures containing *B* serrata, which failed to meet the inclusion criteria for this systematic review, tend to point in the same direction.^{4 5 14} *B* serrata has been used traditionally against inflammatory diseases.¹⁵ Its main pharmacologically active ingredients are α and β boswellic acid, as well as other pentacyclic

WHAT IS ALREADY KNOWN ON THIS TOPIC

Frankincense has a long history of use

Some of its ingredients have anti-inflammatory activity Several clinical trials have been done

WHAT THIS STUDY ADDS

This is a systematic review of data from randomised clinical trials

It shows encouraging results for conditions caused or maintained by inflammation

Several caveats exist and independent replications are needed

triterpenic acids.¹⁶ These compounds have been shown to inhibit pro-inflammatory processes by their effects on 5-lipooxygenase and cyclo-oxygenase and on the complement system.^{15 17}

The evidence evaluated here may be encouraging, but it is not convincing. Not enough large randomised clinical trials have been published for any condition. The medications used in these trials cannot be directly compared in terms of contents and strength. The pharmacokinetics and optimal dose of *B serrata* extracts are largely unknown; usually 600-3000 mg gum resin per day or equivalents are recommended for oral intake.¹⁸ Source of funding or sponsorship was undisclosed in all but one trial.¹³

Dozens of *B serrata* preparations for oral intake are commercially available. The majority are not regulated as medicines but sold as food supplements. Fortunately, the safety profile of *B serrata* seems good.¹⁸ In the included trials, no serious, long term, or irreversible adverse effects were noted. Other data indicate that mild adverse effects such as nausea, acid reflux, and gastrointestinal upset may occasionally occur.¹⁸ No evidence of serious interactions with drugs has been noted.¹⁸ However, absence of evidence is not the same as evidence of absence, which is particularly relevant in herbal medicine, where pharmacovigilance is often less than optimal.¹⁹

Many of the medical, quasimedical, or cosmetic claims made implicitly or explicitly for *B serrata* products are not supported by the available evidence. Their trade names speak for themselves: regeneration body balm, intensive eye serum, supernatural instant youth serum, lifting and firming body lotion, joie de vivre face lotion, radiance anti-ageing, joint and muscle balm, ultra inflammactin, to name a few. Currently more than one million websites on "Frankincense" and half a million on "Boswellia" exist (Google searches, November 2008); the majority fail to offer reliable information on its medicinal uses.

This systematic review has several limitations. Although the search strategy was thorough, some randomised clinical trials might not have been located. A positive publication bias cannot be excluded—complementary medicine journals rarely publish negative results.²⁰ The overall picture generated by a systematic review could thus be false positive. Methods for assessing the extent of publication bias are not very effective if, as in the present case, few trials are available. Mandatory worldwide registration of clinical trials in herbal medicine seems unlikely to happen at present. Incomplete reporting is another problem. One trial related to a subset of patients from a larger multicentre study that has never been published in full.⁸ Crucially, the paucity of rigorous studies prevents any definitive judgement about the effectiveness of *B serrata* extracts.

In conclusion, it might be tempting to buy "instant youth" in the form of a *B serrata* product for Christmas, but sadly the evidence for this claim is nonexistent. For other indications, evidence is encouraging but not convincing. The existing data do, however, warrant further investigation of this herbal medicine.

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- Provenance and peer review: Not commissioned; externally peer reviewed. 1 Hughes K. The incense bible. New York: Haworth Press, 2007.
- 2 Chopra A, Lavin P, Patwardhan B, Chitre D. A 32-week randomized, placebo-controlled clinical evaluation of RA-11, an ayurvedic drug, on osteoarthritis of the knees. J Clin Rheumatol 2004;10:236-45.
- 3 Kulkarni RR, Patki PS, Jog VP, Gandage SG, Patwardhan B. Treatment of osteoarthritis with a herbomineral formulation: a double-blind; placebocontrolled; cross-over study. *J Ethnopharm* 1991;33:91-5.
- 4 Gupta I, Parihar A, Malhotra P, Singh GB, Lüdtke R, Safayhi H, et al. Effects of *Boswellia serrata* gum resin in patients with ulcerative colitis. *Eur J Med Res* 1997;2:37-43.
- 5 Gupta I, Parihar A, Malhotra P, Gupta S, Lüdtke R, Safayhi H, et al. Effects of gum resin of *Boswellia serrata* in patients with chronic colitis. *Planta Med* 2001;67:391-5.
- 6 Jadad AR, Moore RA, Carrol D, Jenkinson C, Reynolds DJM, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials—is blinding necessary? *Contr Clin Trials* 1996;17:1-12.
- 7 Gupta I, Gupta V, Parihar A, Gupta S, Lüdtke R, Safayhi H, et al. Effects of Boswellia serrata gum resin in patients with bronchial asthma: results of a double-blind, placebo-controlled, 6-week clinical study. Eur J Med Res 1998;3:511-4.
- 8 Sander O, Herborn G, Rau R. Is H15 (resin extract of *Boswellia serrata*, "incense") a useful supplement to established drug therapy of chronic polyarthritis? Results of a double-blind pilot study. [German] *Z Rheumatol* 1998;57:11-6.
- 9 Gerhardt H, Seifert F, Buvari P, Vogelsang H, Repges R. Therapy of active Crohn disease with Boswellia serrata extract H 15. [German] Z Gastroenterol 2001;39:11-7.
- 10 Kimmatkar N, Thawani V, Hingorani L, Khiyani R. Efficacy and tolerability of Boswellia serrata extract in treatment of osteoarthritis of knee—a randomized double blind placebo controlled trial. *Phytomedicine* 2003;10:3-7.
- 11 Madisch A, Miehlke S, Eichele O, Mrwa J, Bethke B, Kuhlisch E, et al. Boswellia serrata extract for the treatment of collagenous colitis. A double-blind, randomized, placebo-controlled, multicenter trial. IntJ Colorectal Dis 2007;22:1445-51.
- 12 Sontakke S, Thawani V, Pimpalkhute P, Kabra P, Babhulkar S, Hingorani H. Open, randomized, controlled clinical trial of *Boswellia serrata* extract as compared to valdecoxib in osteoarthritis of knee. *Indian J Pharmacol* 2007;39:27-9.
- 13 Sengupta K, Alluri KV, Satish AR, Mishra S, Golakoti T, Sarma KV, et al. A double blind, randomized, placebo controlled study of the efficacy and safety of 5-Loxin(R) for treatment of osteoarthritis of the knee. Arthritis Res Ther 2008;10:R85. doi:10.1186/ar2461.
- 14 Badria FA, El-Farahaty T, Shabana AA, Hawas SA, El-Batoty MF. Boswellia-Curcumin preparation for treating knee osteoarthritis: a clinical evaluation. Alt Compl Ther 2002;December:341-8.
- 15 Ammon HP. Boswellic acids in chronic inflammatory diseases. Planta Med 2008;72:1100-16.
- 16 Pardhy RS, Bhattacharya SC. Boswellic acid, acetyl-boswellic acid and 11-keto-boswellic acid, four pentacyclic triterpenic acids from the resin of *Boswellia serrata*. *Indian J Chem* 1978;16B:176-8.
- 17 Knaus U, Wagner H. Effects of boswellic acid of *Boswellia serrata* and other triterpenic acids on the complement system. *Phytomedicine* 1996;3:77-81.
- 18 Ernst E, Pittler MH, Wider B, Boddy K. *Complementary therapies for pain management*. Edinburgh: Elsevier Mosby, 2007.
- 19 Ernst E. Challenges for phytopharmacovigilance. Postgrad Med J 2004;80:249-50.
- 20 Ernst E, Pittler MH. Alternative therapy bias. Nature 1997;385:480.

Seasonal medical myths that

A few more medical myths bite the dust, thanks to Rachel Vreeman and Aaron Carroll

In the pursuit of scientific truth, even widely held medical beliefs require examination or re-examination. Both physicians and non-physicians sometimes believe things about our bodies that just are not true. As a reminder of the need to apply scientific investigation to conventional wisdom, we previously discussed the evidence disputing six commonly held medical myths.¹ The holiday season presents a further opportunity to probe medical beliefs recounted during this time of the year. We generated a list of common medical or health beliefs related to the holidays and winter season and searched Medline for scientific evidence to support or refute these beliefs. If we couldn't find any evidence in the medical literature, we searched the internet using Google.

G Sugar causes hyperactivity in children

While sugarplums may dance in children's heads, visions of holiday sweets terrorise parents with anticipation of hyperactive behaviour. Regardless of what parents might believe, however, sugar is not to blame for out of control little ones. At least 12 double blind randomised controlled trials have examined how children react to diets containing different levels of sugar.² None

of these studies, not even studies looking specifically at children with attention-deficit hyperactivity disorder, could detect any differences in behaviour between the children who had sugar and those who did not.³ This includes

sugar from sweets, chocolate, and natural sources. Even in studies of those who were considered "sensitive" to sugar, children did not behave differently after eating sugar full or sugar-free diets.³

Scientists have even studied how parents react to the sugar myth. When parents think their children have been given a drink containing sugar (even if it is really sugarfree), they rate their children's behaviour as more hyperactive.⁴ The differences in the children's behaviour were all in the parents' minds.⁴

Suicides increase over the holidays

Holidays can bring out the worst in us. The combined stresses of family dysfunction, exacerbations in loneliness, and more depression over the cold dark winter months are commonly thought to increase the number of suicides. While the holidays might, indeed, be a difficult time for some, there is no good scientific evidence to suggest a holiday peak in suicides.⁵⁻⁷

One study from Japan that looked at suicides in 1979-94 showed that the rate of suicide was lowest in the days before a holiday and highest in the days after the holiday.8 In contrast, in a study from the United States of suicides over a 35 year period, there was no increase before, during, or after holidays.9 Indeed, people might actually experience increased emotional and social support during holidays. In the US, rates of psychiatric visits decrease before Christmas and increase again afterwards.¹⁰ A smaller study of adolescents showed a peak in suicide attempts at the end of the school year,¹¹ possibly reflecting a decrease in social support. Data from Ireland on suicide in 1990-8 also failed to connect suicides with the holidays.¹² While Irish women were no more likely to commit suicide on holidays than on any other days, Irish men were actually significantly less likely to do so.

Further debunking myths about suicide, people are not more likely to commit suicide during the dark winter months. Around the world, suicides peak in warmer months and are actually lowest in the winter. In Finland, suicides peak in autumn and are lowest in the winter.¹³ In a 30 year study of suicides in Hungary, researchers again found the highest rates of suicides in the summer and the lowest in the winter.¹⁴ Studies of

> suicide rates from India also show peaks in April and May.¹⁵ Studies from the US reflect this pattern, with lower

rates in November and December than in typically warmer months.⁶

Of course, none of this evidence suggests that suicides do not happen over the holidays. The epidemiological evidence just does not support that the holidays are a time of increased risk.

Poinsettia toxicity

With flowers and leaves of red, green, and white, poinsettias are widely used in holiday decorations. Even though public health officials have reported that poinsettias are safe, many continue to believe this is a poisonous plant.¹⁶

In an analysis of 849575 plant exposures reported to the American Association of Poison Control Centers,¹⁷ none of the 22793 cases involving poinsettia

resulted in considerable poisoning.¹⁷ No one died from exposure to or ingestion of poinsettia, and most (96%) did not even require medical treatment. In 92 of the cases, children ingested substantial quantities of poinsettias, but none needed medical treatment, and toxicologists concluded that poinsettia exposures and ingestions can be treated without referral to a healthcare facility.¹⁷ Another study, looking at poinsettia ingestion by rats, could not find a toxic amount of poinsettia, even at amounts that would be the equivalent of 500-600 poinsettia leaves or nearly a kilogram of sap.¹⁸

Excess heat loss in the hatless

As temperatures drop, hats and caps flourish. Even the US Army Field manual for survival



lack convincing evidence

recommends covering your head in cold weather because "40 to 45 percent of body heat" is lost through the head.19 If this were true, humans would be just as cold if they went without trousers as if they

went without a hat. But patently this is just not the case.

This myth probably originated with an old military study in which scientists put subjects in arctic survival suits (but no hats) and measured their heat loss in extremely cold temperatures.²⁰ Because it was the only part of the subjects' bodies that was exposed to the cold, they lost the most heat through their heads. Experts say, however, that had this experiment been performed with subjects wearing only swimsuits, they would not have lost more than 10% of their body heat through their heads.²⁰ A more recent study confirms that there is nothing special about the head and heat loss.²¹ Any uncovered part of the body loses heat and will reduce the core body temperature proportionally. So, if it is cold outside, you should protect your body. But whether you want to keep your head covered or not is up to you.

Nocturnal feasting makes you fat

Holiday feasts and festivities present us with many culinary options. A common suggestion to avoid unwanted weight gain is to avoid eating at night, and at

first glance, some scientific studies seem to support this. In a study of 83 obese and 94 non-obese women in Sweden, the obese women reported eating more meals, and their meals were shifted to the afternoon, evening, or night.22 But just because obesity and eating more meals at night are associated, it does not mean that one causes the other. People gain weight because they take in more calories overall than they burn up. The obese women were not just night eaters, they were also eating more meals, and taking in more calories makes you gain weight regardless of when calories are consumed.

> Other studies found no link at all between eating at night and weight gain. Swedish men did not show any evidence of gaining weight with night time meals.²³ In a study of 86 obese and 61 normal weight men, there were no differences in

the timing of when they ate.²³ Another study of 15 obese people found that the timing of meals did not change the circadian rhythm pattern of energy expenditure.²⁴ In a study of over 2500 patients, eating at night was not associated with weight gain, but eating more than three times a day was linked to being overweight or obese.²⁵ Studies have connected skipping breakfast with gaining more weight, but this is not because breakfast skippers eat more at night.²⁶ Breakfast skippers eat more during the rest of the day. Records of calorie intake suggest that those who eat breakfast maintain healthy weights because their calorie intake is more evenly distributed over the day.^{26 27} In other words, when you eat three regular meals, you are not as likely to overeat at any one particular meal or time.



You can cure a hangover with ...

From aspirin and bananas to Vegemite and water, internet searches present seemingly endless options for preventing or treating alcohol hangovers.²⁸ Even medical experts offer suggestions.29

No scientific evidence, however, supports any cure or effective prevention for

alcohol hangovers. A systematic review of randomised trials evaluating medical interventions for preventing or treating hangovers found no effective interventions in either traditional or complementary medicine.28 While a few small studies using unvalidated symptom scores showed

minor improvements, the conclusion of the exhaustive review was that propranolol, tropisetron, tolfenamic acid, fructose or glucose,

and dietary supplements including borage, artichoke, prickly pear, and Vegemite all failed to effectively "cure hangovers." While more recent studies in rats show some potential for new products to alter mechanisms associated with hangovers,^{30 31} humans also face risks when using certain "hangover cures."32 A hangover is caused by excess alcohol consumption. Thus, the most effective way to avoid a hangover is to consume alcohol only in moderation or not at all.

Conclusions

Examining common medical myths reminds us to be aware of when evidence supports our advice, and when we operate based on unexamined beliefs. This was not a systematic review of either the evidence to refute these medical myths or of doctors' beliefs. None the less, we applied rigorous search methods to compile data, and evidence of the prevalence of these medical beliefs is readily available. Only by investigation, discussion, and debate can we reveal the existence of such myths and move the field of medicine forward.

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Appointments timed in proximity to annual milestones and compliance with screening: randomised controlled trial

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Abstract

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Objective To investigate whether appointments for screening timed in proximity to annual milestones (birthdays, Christmas, and New Year) may be used as a strategy to improve attendance for screening for colorectal cancer. **Design** Randomised controlled trial.

Setting City of Oslo (urban) and Telemark county (urban and rural), Norway.

Participants 12960 screened adults (64.7% of those invited). **Main outcome measure** Attendance rates for each week and month of assigned appointment.

Results Attendance rates were significantly higher in December than the rest of the year (72.3% v 64.6%, P<0.001) in adults who received an invitation in the week of their birthday or were assigned to screening in the first or second week after their birthday (67.9% v 64.5%, P=0.007). This effect was most pronounced in the urban population of Oslo. In a multivariable logistic regression model, attendance improved in those who received an invitation in the week of their birthday or were assigned to screening in the first or second week after their birthday (odds ratio 1.15, 95% confidence interval 1.03 to 1.28) and those who were assigned to screening in December (odds ratio 1.45, 1.16 to 1.82).

Conclusion Attendance rates for screening for colorectal cancer were higher in December and around attendees' birthdays, the latter particularly in an urban population. Compliance with screening programmes may therefore be improved by timing invitations in proximity to annual milestones.

Trial registration Clinical Trials NCT00119912.

Introduction

Age has not been assessed as a motivating factor in screening for colorectal cancer. In a small study of screening using flexible sigmoidoscopy, age was highlighted as a risk factor when invitations for screening were posted. Invitees were given an appointment within weeks after their birthday. The attendance rate in this study (Telemark Polyp Study) was 81%,¹ but it was uncertain if the timing of invitations was important and if this strategy was worth adopting in screening programmes with poor attendance. We investigated whether invitations timed in proximity to annual milestones had an impact on compliance with screening for colorectal cancer in a large Norwegian study during 1999-2001.²

Methods

The Norwegian Colorectal Cancer Prevention Trial 1 is a randomised controlled trial of flexible sigmoidoscopy alone or with faecal occult blood testing as screening modalities.³ Briefly, 20780 adults aged 50-64 from Oslo (urban area) and Telemark (urban and rural), Norway were invited to screening six or seven weeks before the appointment. The control group was the remaining age cohorts not invited in the screening areas. The present study on attendance in relation to annual milestones was not a prespecified analysis of the trial.

We calculated the distribution of appointments according to birth month of invitees and used the χ^2 test for significance. Using logistic regression analysis we determined variables that contributed to attendance (age, sex, screening modality, centre, appointment time, and appointment in relation to birthday) and tested these in univariable analyses before incorporating them in a multivariable model. The association between the variables and attendance was expressed as odds ratios (95% confidence intervals).

Results

Overall, 12960 of 20003 invited adults (64.7%) attended screening. Attendance was higher for women than for men (66.0% v 63.5%, P<0.001) and higher in Telemark than Oslo (71.4% v 58.0%, P<0.001; see bmj.com). In both sexes a higher attendance rate was seen with increasing age–61.6% (age 50-54), 66.4% (55-59), and 66.8% (60-64; P<0.001; see bmj.com).

Weekly attendance showed peaks in the first, second, sixth, and seventh weeks after birthdays; the sixth and seventh weeks corresponding to invitations received in the week of a birthday. Overall, 1095 of 1613 (67.9%) participants assigned to screening in the first, second, sixth, and seventh weeks after birthdays attended for screening compared with 11866 of 18390 (64.5%) assigned in any other week (P=0.007). In a subgroup analysis this difference was statistically significant in Oslo.

Attendance according to calendar month was significantly different, with 72.3% attending in December (highest) and 62.5% in March (lowest; table). In Oslo, attendance in December compared with the rest of the year was 66.8% v 57.8% (P=0.003) and in Telemark was 79.3% v 71.2% (P=0.009).

A multiple logistic regression analysis confirmed the univariable analyses, with a significant improvement in attendance shown in December (adjusted odds ratio 1.45, 95% confidence interval 1.16 to 1.82, P=0.001). The adjusted odds ratio for attendance when given an appointment in the first, second, sixth, or seventh weeks after a birthday compared with any other week was 1.15 (95% confidence interval 1.03 to 1.28; P=0.01). Independent predictors of attendance were age, female sex, screening modality, and area of residence (table).

Discussion

Compliance with screening for colorectal cancer in Norway was significantly increased in adults invited for screening in December and close to their birthday.

The strength of this study is its large size and population

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Logistic regression with odds ratio for attendance at screening for colorectal cancer in Norway

Variable	No of examinations	Attendance rate (%)	Crude odds ratio (95% CI)	Adjusted odds ratio* (95% CI)	P value
Screening weeks related to birthday:					
Any but weeks 1, 2, 6, and 7 after birthday†	18 390	64.5	Reference	_	
1, 2, 6, or 7 after birthday†	1613	67.9	1.16 (1.04 to 1.30)	1.15 (1.03 to 1.28)	0.01
Month of screening‡:					
January	2012	65.7	Reference	_	
February	2028	65.1	0.98 (0.86 to 1.11)	1.00 (0.87 to 1.14)	0.95
March	1915	62.5	0.87 (0.76 to 0.99)	0.88 (0.77 to 1.00)	0.06
April	1452	63.7	0.92 (0.80 to 1.06)	0.96 (0.83 to 1.11)	0.57
Мау	1857	66.1	1.02 (0.89 to 1.16)	1.07 (0.93 to 1.23)	0.33
June	1502	63.6	0.91 (0.79 to 1.05)	0.95 (0.82 to 1.09)	0.47
August	2129	63.6	0.91 (0.80 to 1.03)	0.92 (0.81 to 1.04)	0.19
September	2282	65.8	1.00 (0.88 to 1.14)	1.01 (0.89 to 1.14)	0.93
October	2224	65.2	0.98 (0.86 to 1.11)	1.01 (0.89 to 1.15)	0.86
November	2118	64.1	0.93 (0.82 to 1.06)	0.98 (0.86 to 1.11)	0.74
December	484	72.3	1.36 (1.10 to 1.70)	1.45 (1.16 to 1.82)	0.001

FS=flexible sigmoidoscopy

*Adjusted for age, sex, screening modality, screening centre, allotted time for screening in weeks 1, 2, 6, or 7 after birthday and month for allotted screening appointment. tWeeks 6 and 7 for screening appointment correspond to invitations received in birthday week.

 \pm P=0.009 (χ^2) for attendance in January to December. No screening in July because of summer holidays.

based design. A weakness is the generalisability of the findings to other countries, as the Norwegian population studied may differ from other populations. Furthermore, appointments in December, unlike the other months, were limited to the first two weeks because of the holidays. When attendance in December was analysed with the first and second weeks in any other month, however, it remained high (data not shown). Since the present analysis was not prespecified, the results should be considered as generating a hypothesis rather than as definitive. The identification and reduction of barriers to screening is one way to improve attendance,^{4 5} another is to try to identify factors associated with high attendance. Both the Telemark Polyp Study 1 and the present larger study using flexible sigmoidoscopy had high attendance rates in Telemark (81% and 71%). These attendance rates are high compared with the population coverage in similar trials in the United Kingdom (39%) and Italy (26%)^{6 7} and in Swedish and Danish trials (30-47%).^{8 9} Whereas the Telemark study used invitations timed near birthdays, the Norwegian Colorectal Cancer Prevention trial 1 randomly invited adults throughout the year.

In the present study we explored the potential for timed invitations to improve attendance at screening, and we focused on annual milestones. Birthdays and Christmas and New Year are two poignant reminders of ageing. We did not mention age as a risk factor in the invitations, so the distribution of attendance rates in relation to birthdays suggests that appointments allocated shortly after birthdays or invitations received in the week of a birthday have the potential to improve compliance with screening. The Norwegian cancer prevention trial did not emphasise age as a risk factor. The higher attendance in Oslo when an appointment was given in the first or second week after a birthday or when the invitation was received in the week of a birthday is most likely due to inherent differences between an urban population (Oslo) and an urban and rural one (Telemark).

Birthday related screening appointments for colorectal

cancer were associated with a 4.3% increase in attendance in Oslo and a 2.2% increase in Telemark. By allocating appointments in December the corresponding gain in attendance was 9.0% and 8.1%, respectively. What this may imply for intention to treat analyses on incidence of colorectal cancer and mortality reduction may depend on the rate of attendance.¹⁰ In the Norwegian colorectal cancer prevention trial, the addition of faecal occult blood testing to flexible sigmoidoscopy resulted in a 4% drop in attendance, from 67% to 63%. In an intention to diagnose analysis of diagnostic gain this drop could not be compensated by a presumed higher sensitivity of the combined screening modalities.²

It has been argued that high attendance in Norwegian trials of screening for colorectal cancer may not be comparable to other countries. The only trial of screening using faecal occult blood testing in Norway, at the time when 81% attendance was obtained for flexible sigmoidoscopy in the Telemark study, had a compliance of $55\%^{11}$; comparable to other trials of faecal occult blood testing. This suggests that screening programmes in Norway face similar barriers and facilitators as other countries.

Adjusted odds ratios in the logistic regression analysis

WHAT IS ALREADY KNOWN ON THIS TOPIC

Poor compliance with cancer screening is a main barrier to successful screening programmes

Adequate measures to improve compliance of the target population are difficult to identify

Age is a major risk factor for colorectal cancer, and studies have consistently shown that compliance with screening increases with age

WHAT THIS STUDY ADDS

Compliance with screening can be improved by timing appointments close to birthdays and in December Although the reasons for this are unclear they might relate to reminders of ageing triggered by annual milestones such as birthdays of material from the Norwegian colorectal cancer prevention trial showed that age, female sex, flexible sigmoidoscopy alone, and area of residence remained independent determinants of attendance. These variables are known predictors of compliance with screening.^{6 8 9 12}

Conclusion

In the Norwegian colorectal cancer prevention trial, attendance for screening increased with age and was higher for those given an invitation in the week of their birthday or an appointment in the first or second week after their birthday—an effect that seemed statistically significant to the urban population of Oslo. A higher attendance in December was observed in Oslo and Telemark. Playing on perception of age or annual milestones might help improve compliance with screening. We suggest that screening programmes should consider the potential benefits of timing appointments in the first or second weeks after birthdays and extending working hours in December.

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- Hoff G, Thiis-Evensen E, Grotmol T, Sauar J, Vatn MH, Moen IE. Do undesirable effects of screening affect all-cause mortality in flexible sigmoidoscopy programmes? Experience from the Telemark polyp study 1983-1996. *EurJ Cancer Prev* 2001;10:131-7.
- 2 Gondal G, Grotmol G, Hofstad B, Bretthauer M, Eide TJ, Hoff G. The Norwegian colorectal cancer prevention (NORCCAP) screening study: baseline findings and implications for clinical work-up in age groups 50-64 years. Scand J Gastroenterol 2003;38:635-42.
- 3 Bretthauer M, Gondal G, Larsen IK, Carlsen E, Eide TJ, Grotmol T, et al. Design, organization and management of a controlled population screening study for detection of colorectal neoplasia. *Scand J Gastroenterol* 2002;37:568-73.
- 4 Petersen G. Barriers to preventive intervention. *Gastroenterol Clin NAm* 2002;31:1061-8.
- 5 Dulai GS, Farmer MM, Ganz PA, Berbaards CA, Qi K, Doetrich AJ, et al. Primary care provider perceptions of barriers to and facilitators of colorectal cancer screening in a managed care setting. *Cancer* 2004;100:1843-52.
- Segnan N, Senore C, Andreoni B, Aste H, Bonelli L, Crosta C, et al. Baseline findings of the Italian multicenter randomised controlled trial of "once-only sigmoidoscopy"—SCORE. J Natl Cancer Inst 2002;94:1763-72.
- 7 UK Flexible Sigmoidscopy Screening Trial Investigators. Single flexible sigmoidoscopy screening to prevent colorectal cancer: baseline findings of a UK multicentre randomized trial. *Lancet* 2002;359:1291-300.
- 8 Blom J, Liden A, Jeppson B, Holmberg L, Påhlman L. Compliance and findings in a Swedish population screened for colorectal cancer with sigmoidoscopy. *Eur J Surg Oncol* 2002;28:827-31.
- 9 Rasmussen M, Kronborg O, Fenger C, Jørgensen OD. Possible advantages and drawbacks of adding flexible sigmoidoscopy to Hemoccult-II in screening for colorectal cancer. Scand J Gastroenterol 1999;34:73-8.
- 10 Hoff G. Colorectal cancer screening: review of the evidence and suggestions on when and how to move on from randomized trials to screening programmes. *Scand J Gastroenterol* 2004;39:99-103.
- 11 Dybdahl JH, Haug K, Bakkevold K, Olsen KO, Vetvik K. Screening for occult faecal blood loss in a community by means of Hemoccult-Il slides and a tetramethylbenzindine test. *Scand J Gastroenterol* 1984;19:343-9.
- 12 Wardle J, Miles A, Atkin W. Gender differences in utilization of colorectal cancer screening. *J Med Screen* 2005;12:20-7.

Washerman's elbow (Oh, yes it is!)

My patient, Mr Monie, aged 36 years, came to see me in March and complained of a painful left elbow. The pain had been present for a month or so, and he was not aware of any injury that might have caused it. There was no medical history of note, he took no drugs and was generally fit and well. I knew he was an actor by profession, but this seemed irrelevant to his complaint.

On examination there was no swelling, palpation revealed a tenderness over the lateral epicondyle made worse by gripping, and the patient had full range of movement. I said that it seemed to be a sort of tennis elbow, but it was unclear how it had arisen. I advised rest in a general sort of way, and Mr Monie seemed rather unimpressed by the diagnosis and its management.

As a way of ending this slightly unsatisfactory consultation, I asked whether he was working at present. He told me that he had recently finished a pantomime run of *Aladdin*



A scene from *Aladdin* with Chris Harris as Widow Twankey, the mangle, and Jon Monie as Wishee-Washee. Reproduced with permission of UK Productions

in which he had taken the part of Wishee-Washee. He said it had gone rather well, particularly the business with the mangle.

I paused and asked for details. Twice nightly, six days a week for seven weeks, he had lifted the upper mangle roller with his right hand and then, leading with his left, had been forced through the rollers into a basket—to the great delight of the audience.

Armed with this history, I confidently diagnosed an unusual work related upper limb disorder (WRULD) to the mutual satisfaction of patient and doctor. I advised that the prognosis was good providing mangling was avoided. He's taken my advice. This year perhaps Simple Simon in *Jack and the Beanstalk* at the Theatre Royal, Bath, starting in December. Early booking is advised.

My learning points from this episode:

- a) A job title is an insufficient occupational history. More information may be gathered by finding out what patients actually do in the course of their work.
- b) Most workers with an occupational disorder first consult their general practitioner,¹ and colleagues may find the Society of Occupational Medicine website (som.org.uk) of interest
- c) It is worth making time for chitchat.

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Patient consent obtained, and permission to reveal names and roles.

- Snashel D. Hazards of work. In: ABC of occupational medicine. London: BMJ Publishing Group, 1997.
- Cite this as: BMJ 2008;337:a2138