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Funding Opportunity

Operating Grant 2011-03-01

Application Number 245851 **ResearchNet ID** 122018

Suggested Peer Review Committees

1st: Public, Community & Population Health

2nd: Health Services Evaluation & Interventions Research

Nominated Principal Applicant

Surname	Given Names	PIN
HANLEY	James	21088

Project Title

Methods to measure (and measures of) the (actual) mortality reductions produced by cancer screening.

Relevant Research Area:	Title of Priority Announcement/Funding Pools:
Breast Cancer	Breast Cancer

Linked Programs:

Canadian Institutes of Health Research | Instituts de recherche en santé du Canada

PROTECTED WHEN COMPLETED

Appl. # 245851

Application Details

Funding Opportunity:
Operating Grant: 2010-2011 (2011-03-02)

Proposed Start Date:

Nominated Principal Applicant/Candidate:

Surname: HANLEY Given Names: James

Institution: McGill University/Université McGill
Faculty: Faculty of Medicine
Department: Epidemiology and Biostatistics

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Project Title:
Methods to measure (and measures of) the (actual) mortality reductions produced by cancer screening.

Primary location where research to be conducted: McGill University/Université McGill

Faculty: Faculty of Medicine Department: Epidemiology and Biostatistics

Institution which will administer project funds (Institution Paid):

McGill University/Université McGill

Period of support requested: 3 **Year(s)** _____ **Month(s)**

THE FOLLOWING SECTIONS ARE NOT APPLICABLE TO ALL PROGRAMS

Budget section - Amounts Requested from CIHR in the First Full Year:
Operating: 82800 Equipment: 1500 Total Amount Requested: 84300

☑ New ☐ Renewal Funding Reference Number (FRN):

Is this application a resubmission of a previously unsuccessful new application? ☐ Yes ☑ No

Is this application a resubmission of a previously unsuccessful renewal application? ☐ Yes ☑ No FRN #:

Have you applied to this program in the last two years? ☐ Yes ☐ No

Is this a multi-center study? ☐ Yes ☑ No

*** For Administrative Purposes Only**

RN #: 122018

RELEVANCE FORM | FORMULAIRE DE PERTINENCE

Title of Research Proposal I Titre de la proposition de recherche :

Methods to measure (and measures of) the (actual) mortality reductions produced by cancer screening.

Relevant Research Area |Thème de recherche pertinent *:*

Breast Cancer

Title of Priority Announcement/Funding Pool | Titre de la demande d'Annonce de priorités/Classe de financement :

Breast Cancer

Description | Description :

Screening is one of the key tools for reducing breast cancer mortality.

Unfortunately, previous analyses of the data from screening trails has led to misleading underestimates of how much a sustained screening program can reduce mortality.

The results of our re-analyses, based on the timing of the deaths in trials in relation to when screening was performed, will give more useful estimates of what any specified screening schedule should produce. This permanent steady state reduction is likely to be a lot larger than the estimates, based on cumulative mortality, which have been produced using the prevailing data-analysis methods.

The results will be of use to program planners, and allow them to better rank various programs for cancer mortality reduction.

Other Applicants

Surname	Given Names	Role
Dendukuri	Nandini	Co-Applicant
Institution	**Department**	**Faculty**
McGill University/Université McGill	Epidemiology and Biostatistics	Faculty of Medicine

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Strumpf	Erin	Co-Applicant
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McGill University/Université McGill	Economics	Faculty of Arts and Science

Surname	Given Names	Role
Institution	Department	Faculty

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Surname	Given Names	Role
Institution	Department	Faculty

Surname	Given Names	Role
Institution	Department	Faculty

Lay title of the research

Methods that more accurately answer the question: how many fewer cancer deaths are there (would there be) each year in Canada (and elsewhere) as a result of cancer screening?

Abstract suitable for preparation of a press release

We spend a lot on screening. We can count the dollars and document the harms to individuals. Sadly, despite many long costly trials involving large numbers of people, policy makers, funders and the public do not confidently know how much these programs have (or would) cut the numbers of breast, colon, prostate, and lung cancer deaths.
One reason is the metric used, which averages over the full (but arbitrary) period of follow-up. This metric is suitable for interventions that result in virtually immediate and long-lasting reductions in sickness and death rates, such as adult circumcision, HPV/polio vaccine, or screens for abdominal aneurysms. However, it mis-measures the delayed effect of screening. The benefit of screening seen in 2011 is not due to screens done in 2011, but earlier ones. Returns on 2011 screens will emerge in mid, but mostly the late 2010s. The usual metric ignores critical timing information and badly underestimates the impact of a screening program. Naively pooling results from several trials further dilutes it.
We will extend the method we developed to re-analyze data from the European Prostate Cancer Screening trial. Our method estimates the yearly benefit of a screening program by summing returns on past financial investments. Using this method, we estimated that the reduction in mortality was 50% beyond year 7, much lower than the 20% reduction first reported. We will refine our method to handle data from trials with varying schedules, thus making proper use of all available data. We will test the methods on simulated situations where we know the correct answer. We will also apply it to data from all completed trials on breast, colon and lung cancer and report the results in a meaningful way. We will also develop methods for planning the size of new screening trials. The methods described in this proposal will give policy makers and funders more accurate and relevant data on how effective cancer screening programs are/could be.

Project Descriptors *

cancer, screening, biostatistics, parameter-estimation, likelihood methods to combine data, new statistical methods, data extraction, sample sizes

Areas of Research *	**Classification Codes ***
Primary HEALTH SERVICES RESEARCH	Primary BIOSTATISTICS
Secondary CANCER	Secondary

Themes *	**Categories ***
1st Health systems/services	1st Health Services and Policy Research
2nd Social/Cultural/Environmental/Population Health	2nd Population and Public Health
3rd	3rd Cancer Research
4th	4th

Suggested Peer Review Committees:

1st Public, Community & Population Health

2nd Health Services Evaluation & Interventions Research

Suggested External Referee(s)*

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Summary of Research Proposal/Résumé de la proposition de recherche

Background: Canada devotes a lot of resources to screening programs for cancer. It is straightforward to measure their costs, both monetarily and in unintended consequences for individuals. However, despite several long randomized clinical trials (RCTs) evaluating screening (in cancers of the breast, colon, prostate and lung) involving large numbers of subjects, we do not have good answers to the question of how large the intended consequences, such as reduction in cancer mortality, are. Policy makers and program funders are thus faced with a wide array of uncertain and conflicting figures. Worse, the public has become more confused by different pronouncements from various authorities – all with access to the same data.

Much of the confusion has to do with the metric used: the percentage reduction in morbidity/mortality, averaged over the entire period of follow-up -- whatever that period, or the length of follow-up, is. This metric is appropriate for medical treatment trials that measure the virtually immediate and often long-lasting reductions in morbidity/mortality caused by (say) adult circumcision, or an HPV/polio vaccine, or a screen for abdominal aortic aneurysms. It is not appropriate for measuring the reductions produced by screening: unlike aneurysms, the cancers *for which screening made the difference* do not pose an *immediate* threat; rather they *would have proven fatal several years after* they were in fact screen detected (at a curable stage).

Unfortunately, this misleading single-number 'percent reduction' metric is used in all screening trials. It ignores when in time deaths occur, how long after the first or last screen, and how many rounds of screening there were. It seriously dilutes (underestimates) the potential mortality impact of an organized population screening program. Several 'meta-analyses' have merged data across trials, but ignored the timing of the cancer deaths vis-a-vis when and how often people were screened, and the different lengths of follow-up.

To answer the question "how many fewer cancer deaths are there *this year* in Canada (and elsewhere) as a result of cancer screening?" we do not ask how much screening there is this year, and how effective it is; rather, we ask how much screening was going on several years ago, and how effective it was. Depending on the cancer, the returns from screening today (i.e., in the early 2010s) will emerge at the earliest by the mid- but mostly by the late 2010's.
Plan: This project builds on the statistical method used to re-analyze the available data from the ERSPC: European Randomized Screening trial for Prostate Cancer (the re-analysis found a much larger reduction (50% in years 7 and beyond) than the average of 20% that was originally reported, but was hampered by small amounts of information available for the years where the maximum impact is expected: i.e. years 7-12 after screening started). At its core are 3 parameters: the mean and spread of the delay between each screen and its mortality benefit, along with the maximum 'depth' of the mortality deficit created by each round. From these, one can work out how many fewer cancer deaths there would be *each year* as a result of a cancer screening program of a given intensity applied to a given population age range.

We will refine and test the statistical method to handle data from one trial involving countries/populations with different screening schedules (and age ranges) – as in the ERSPC, and to properly merge the data from several trials. We will use statistical convolution (i.e., we add together the mortality deficits which become manifest in a given year, but were produced by different earlier rounds of screening, as one would estimate the total returns accruing this year from financial investments made in different earlier years), and we will add log-likelihoods to combine the data from different studies. This doesn't increase the number of estimated parameters that govern the performance of any specified program (each year-age-arm-study has its own row in the 'design matrix').

We will first test the statistical methods on simulated data where we 'know' what the correct answer should be. We will then gather the necessary data from the RCT's that have been completed for breast, colon, prostate and lung cancer. The data will be the two-dimensional (i.e., age- and year-since-first-screen- specific) numbers of cancer-specific deaths, with the corresponding numbers of person years of experience. Finally, we will develop guidelines for the sample sizes necessary to plan the size of future trials of cancer screening that will use the proposed data-analysis methods. **SIGNIFICANCE:** The methods and analyses will give policy makers and funders more accurate and relevant data on how effective cancer screening programs are/could be.

Lay abstract/Résumé non scientifique

We spend a lot on screening. We can count the dollars and document the harms to individuals. Sadly, despite many long costly trials involving large numbers of people, policy makers, funders and the public do not confidently know how much these programs have (or would) cut the numbers of breast, colon, prostate, and lung cancer deaths.
One reason is the metric used, which averages over the full (but arbitrary) period of follow-up. This metric is suitable for interventions that result in virtually immediate and long-lasting reductions in sickness and death rates, such as adult circumcision, HPV/polio vaccine, or screens for abdominal aneurysms. However, it mis-measures the delayed effect of screening. The benefit of screening seen in 2011 is not due to screens done in 2011, but earlier ones. Returns on 2011 screens will emerge in mid, but mostly the late 2010s. The usual metric ignores critical timing information and badly underestimates the impact of a screening program. Naively pooling results from several trials further dilutes it.
We will extend the method we developed to re-analyze data from the European Prostate Cancer Screening trial. Our method estimates the yearly benefit of a screening program by summing returns on past financial investments. Using this method, we estimated that the reduction in mortality was 50% beyond year 7, much lower than the 20% reduction first reported. We will refine our method to handle data from trials with varying schedules, thus making proper use of all available data. We will test the methods on simulated situations where we know the correct answer. We will also apply it to data from all completed trials on breast, colon and lung cancer and report the results in a meaningful way. We will also develop methods for planning the size of new screening trials. The methods described in this proposal will give policy makers and funders more accurate and relevant data on how effective cancer screening programs are/could be.

Methods to measure (and measures of) the (actual) mortality reductions produced by cancer screening

Contents *page*

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1 INTRODUCTION and BACKGROUND

1.1 Setting, context, and importance

Canada devotes a lot of resources to screening programs for cancer. It is straightforward to measure both the direct monetary costs and the 'collateral' harms. Despite several randomized clinical trials (RCTs) covering many years and a large numbers of subjects, we do not have a good understanding of how large the intended consequences are – specifically the reduction in cancer mortality. Policy makers and funders are thus faced with a wide array of uncertain and conflicting figures (15 years ago, the literature suggested reductions produced by mammography screening of women over age 50 in the 20-40% range; today, some authorities say that they are less than 10% or that there is no evidence they even exceed 0%. Worse, the public has become confused by different advice from various authorities.

Before implementing an expensive organized program for the earlier detection and treatment of a cancer, policymakers need good estimates of the mortality reductions and other savings that will result, in order to weigh these benefits against the costs. Individuals contemplating being screened must also consider this tradeoff. However, as in the recently reported European Randomized Study of Screening for Prostate Cancer (ERSPC)[1], the *reported* reductions from many such trials have been modest, as have estimates based on meta-analyses (prostate, breast and colon cancer)

In some trials, the modest/absent reductions are not surprising, given the weak nature of the screening tools. But there are also methodological reasons in many cases. A few studies employed just 1 round of screening, even if this regimen was not what would be used in "service" screening. Some such studies produced a clear reduction, whereas others did not. In yet other trials, short follow-up periods have prevented the full mortality reductions from being expressed, or reliably measured. Moreover, for funders, the question is not whether the mortality reduction is 'almost definitely' nonzero (i.e., was $p < 0.05$), but *instead* "how many fewer cancer deaths are there *this (and each)* year in Canada as a result of cancer screening?"

This research project seeks to redress a critical aspect of the data-analysis and reporting of RCTs, even when the length of follow-up has been ample. Virtually all reports have effectively averaged across

the entire follow-up, thus merging (i) the (expected) zero-reductions early in follow-up and (ii) the non-zero mortality reductions that emerge later, and presented this average as a single-number summary measure: e.g., a 20% reduction in mortality – over an average of 9 years (range 5-15) in the ERSPC (PSA every 4 years) and 5.5 years (range 5-8) in the National Lung Screening Trial (NLST, 3 spiral CT scans, a year apart). This simplistic measure systematically dilutes the estimate of the mortality reductions produced by screening. In the case of prostate cancer, with its long sojourn times, the underestimation is considerable. In a few instances[2 3], the estimate has been diluted further by including an excessive amount of follow-up time in the calculation: i.e., by averaging not just (i) and (ii) but (i), (ii) and (iii) the further (expected) zero-reductions seen in the years long after the last round of screening could have had any effect.

Despite the clear principles for measuring a screening's impacts set out a generation ago in the classic textbook,[4] our review[5] (appendix) has found that an inappropriate summary measure, which has become predominant over the past 20 years, has lead to considerable underestimates. Throughout the review, we reiterate how data from cancer screening studies can be appropriately analyzed by attention to time-specificity. A second big limitation of the reporting of trials is the failure to include estimates of the critical parameters that would begin to allow one to answer the question "how many fewer cancer deaths are there *this year* in Canada (and elsewhere) as a result of (past) cancer screening?" or "how many fewer cancer deaths will there be in the 2020s in Canada if we start to screen in 2012 and continue to screen every *x* years?"

We focus, as funders would wish to, on the numbers of cancer deaths if a population is subjected to a screening program versus if it is not, and on how trial data, combined with reasonable assumptions, can be used to project the reduction expected from the implementation of such a program. We use the ERSPC to illustrate how data from screening trials should be analyzed, *objectively*, *time-specifically*, and *collectively*. We seek to replace the prevailing data-analysis practices that have also led to serious underestimation in trials of screening for breast, colorectal and lung cancer, and to provide more accurate estimates of what screening is capable of, and within what timeframe, in these areas. The methods we will develop and refine will also improve the design and analysis of future screening trials.

Our *ultimate objective* is to enable planners to use 3 core parameters, which describe the impact of 1 round of screening, to project what effect (in terms of steady state mortality reductions) would be achievable in the future if a specified regimen of screening (not necessarily the one used in past trials) employing that regimen of screening were started today, or is already being achieved using this regimen in a program that has been in operation for some time already.

Moreover, in lieu of new RCT data, we expect to see more analyses using population screening data. Thus it is critical that the time-specificity principle (in both screening time and age) be better understood. Also, we wish to emphasize the value of quantifying the effect of 1 round of screening. Although this quantity will often by hypothetical, it determines the effect of a longer sequence of such rounds, and so it is key that we have appropriate methods to estimate it from broader data.

1.2 In which cases of cancer does screening make a mortality difference?

The degree to which a prostate cancer screening program reduces cancer mortality can be measured by the difference in the numbers of fatal cancers under the "screening absent" and "screening present" scenarios, respectively. *This difference occurs among the 'otherwise fatal' cancers*, i.e., among those that would have proved fatal despite treatment at the time they would have presented clinically. *Cancers that would be cured by treatment at the time of clinical presentation do not affect this difference*.

1.3 Bridging the differences between RCTs and screening programs:

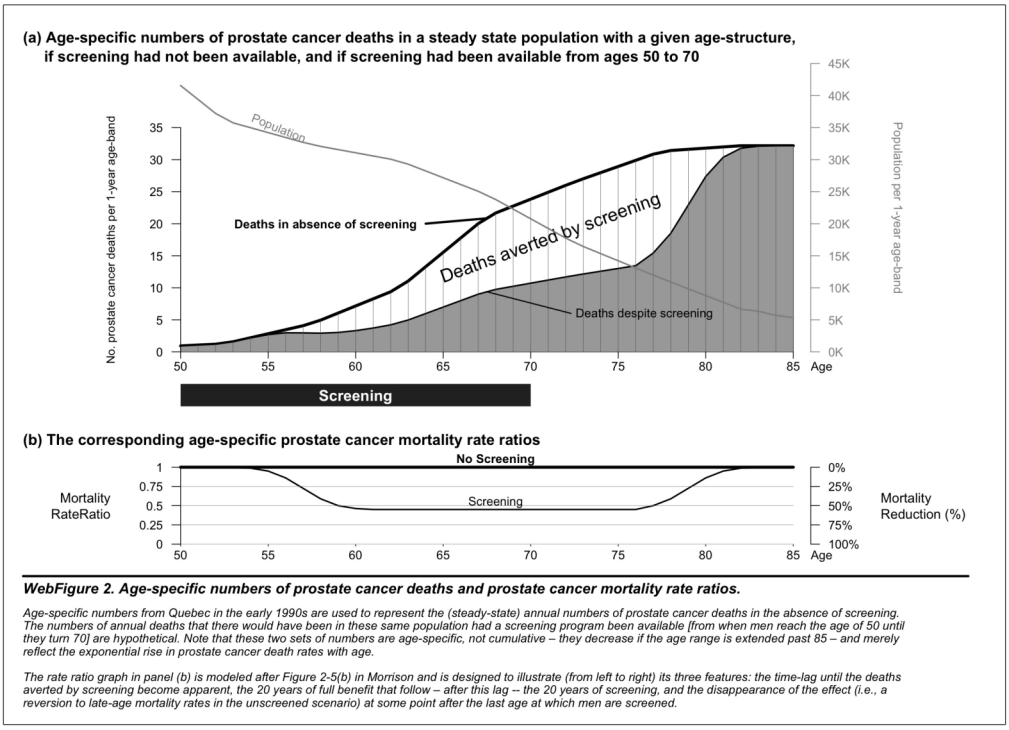
The way results *of trials of screening need to be translated so that they apply to actual screening programs* can be understood via WebFigure 2, which we had used in our review[5].

In *actual trials*, such as the ERSPC, previously-unscreened men of different ages are enrolled and followed in a screening or control arm; an (ideally, high) percentage of men in the screening and an

(ideally, low) percentage of men in the control arms are screened at each round. Screening is terminated after a number of rounds, and data are analyzed some (usually not pre-specified) number of years after the first men were invited. In *practice*, screening in a non-research setting ("service" screening) would be carried out differently: men may be invited to be screened once they turn say 50, and repeatedly until say 70. Of interest is how many fewer cancer deaths there would be annually, *under steady-state conditions*, in the age range say 55 to 80, under this program. This comparison is shown in WebFigure 2(a). The ultimate aim is to obtain rate ratio curves of the type shown in WebFigure 2(b), which is modeled after Figure 2-5(b) in Morrison.[4]

Time-curve 2(b) is central for two reasons. First, it reminds us that the mortality reductions produced by screening and earlier treatment of cancer do not, and can not, become apparent immediately after screening commences: if the cancer, "cured" today *because of* earlier (screening based) detection, had *not* been treated in time, it would have only have proved fatal *several years in the future*. For some cancers, the delay is considerable. Despite this delay of several years, most analyses of data from both trials and non-experimental (cohort-type) studies merge the deaths in this 'early no-reduction' window with those in the time- or age-window when reductions do become apparent. (Interestingly, case-control studies consider the *latency* between exposure to a disease-causing agent and the occurrence of a disease, and between the earlier treatment [prompted by screening] and the time when the cancer would otherwise prove fatal[2].) Nor can reductions produced by screening and earlier treatment of cancer persist indefinitely after screening is discontinued; despite this, some analyses of data from screening trials have also merged the deaths in this 'late no-reduction' window with those from the time- or age-window when reductions would have been apparent[3 2].

Second, *the curve in WebFigure 2(b) can be estimated from screening trials*. This curve can then be applied to the 'no-screening' curve of umbers of deaths in Figure2(a) to yield an estimate of the 'screening' curve of numbers of deaths in Figure2(a). The differences between the two curves of numbers of deaths can then be used to derive the absolute impact of different versions of the screening program.



WebFigure 2. Age-specific numbers of prostate cancer deaths and prostate cancer mortality rate ratios.

Age-specific numbers from Quebec in the early 1990s are used to represent the (steady-state) annual numbers of prostate cancer deaths in the absence of screening. The numbers of annual deaths that there would have been in these same population had a screening program been available [from when men reach the age of 50 until they turn 70] are hypothetical. Note that these two sets of numbers are age-specific, not cumulative – they decrease if the age range is extended past 85 – and merely reflect the exponential rise in prostate cancer death rates with age.

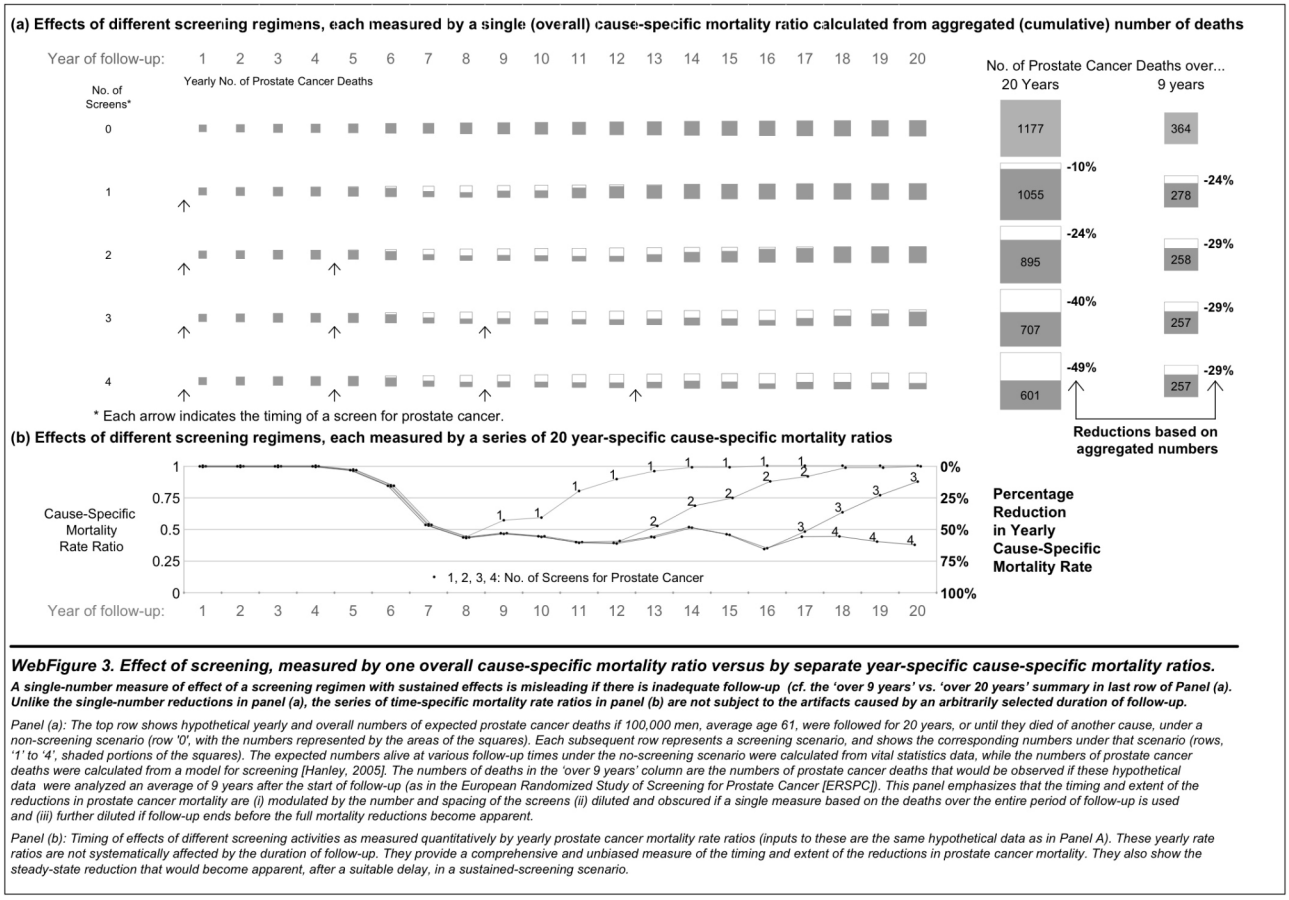
The rate ratio graph in panel (b) is modeled after Figure 2-5(b) in Morrison and is designed to illustrate (from left to right) its three features: the time-lag until the deaths averted by screening become apparent, the 20 years of full benefit that follow – after this lag -- the 20 years of screening, and the disappearance of the effect (i.e., a reversion to late-age mortality rates in the unscreened scenario) at some point after the last age at which men are screened.

Going from (b) to (a) requires some assumptions. In the curve from a typical trial, the 't_0' -- the time of the 1st screen -- refers to a different age-at-1st-screen for different participants: in the ERSCP, the age-range at intake was 55-69. In the 'service' curves in 2(a), there is a common 't_0': age 50 at 1st screen.

1.4 Why time-aggregation in cancer screening trials dilutes

WebFigure 3 shows that, unlike an *overall* ratio, *time-specific* mortality rate ratios directly and unbiasedly measure the timing and magnitude of the reductions produced by different screening regimens, and are not affected by the length of follow-up.

The dilution caused by including those that occur *before* (rather than after[4, 6 7]) this window was only recognized recently[8 2] but the message to avoid it has gone unheeded. Also, analysts have overlooked an additional dilution inherent in the prevailing 'single number summary' measure: this attenuation is highlighted by the entries in the "over 9 years" column. Whereas the numbers of cancer deaths in a traditional trial are *larger* proximal to the entry time, the corresponding numbers in a screening trial are *smaller* at this end of the timescale and larger at the other end. *Thus, the shorter and more inadequate the follow-up, the more heavily is the overall percentage reduction over this period (incorrectly) weighted towards the lesser reductions in these early follow-up years*



WebFigure 3. Effect of screening, measured by one overall cause-specific mortality ratio versus by separate year-specific cause-specific mortality ratios.

A single-number measure of effect of a screening regimen with sustained effects is misleading if there is inadequate follow-up (cf. the 'over 9 years' vs. 'over 20 years' summary in last row of Panel (a). Unlike the single-number reductions in panel (a), the series of time-specific mortality rate ratios in panel (b) are not subject to the artifacts caused by an arbitrarily selected duration of follow-up.

Panel (a): The top row shows hypothetical yearly and overall numbers of expected prostate cancer deaths if 100,000 men, average age 61, were followed for 20 years, or until they died of another cause, under a non-screening scenario (row '0', with the numbers represented by the areas of the squares). Each subsequent row represents a screening scenario, and shows the corresponding numbers under that scenario (rows, '1' to '4', shaded portions of the squares). The expected numbers alive at various follow-up times under the no-screening scenario were calculated from vital statistics data, while the numbers of prostate cancer deaths were calculated from a model for screening [Hanley, 2005]. The numbers of deaths in the 'over 9 years' column are the numbers of prostate cancer deaths that would be observed if these hypothetical data were analyzed an average of 9 years after the start of follow-up (as in the European Randomized Study of Screening for Prostate Cancer [ERSPC]). This panel emphasizes that the timing and extent of the reductions in prostate cancer mortality are (i) modulated by the number and spacing of the screens (ii) diluted and obscured if a single measure based on the deaths over the entire period of follow-up is used and (iii) further diluted if follow-up ends before the full mortality reductions become apparent.

Panel (b): Timing of effects of different screening activities as measured quantitatively by yearly prostate cancer mortality rate ratios (inputs to these are the same hypothetical data as in Panel A). These yearly rate ratios are not systematically affected by the duration of follow-up. They provide a comprehensive and unbiased measure of the timing and extent of the reductions in prostate cancer mortality. They also show the steady-state reduction that would become apparent, after a suitable delay, in a sustained-screening scenario.

Rather than use hypothetical descriptions (as in WebFigure 3), we motivate our plans by briefly reviewing the deficiencies of (alternatives to) prevailing data-analysis practice in actual trials.

1.5.1 Past screening trials: Prostate Cancer:

Our review[5] discussed the main features of the 5 reported trials of PSA screening, but focused on the ERSPC, since its larger sample size and the substantial difference in the participation rates in the two arms meant that only it has any substantial 'resolving power.'

The NEJM ERSPC report[1] expressed the effect of screening on prostate cancer mortality as 1 number, derived from the numbers of prostate cancer deaths over the *entire* period of observation available for each man (range 3-15, average 9 years): 214 prostate cancer deaths in 643,401 man-years of observation in the screening arm and 326 in 785,585 man-years in the control arm. These led to the reported rate ratio of 0.80, and the conclusion that "PSA-based screening reduced the rate of death from prostate cancer by 20%" [95% CI: 2% to 35%].

Our re-analysis[9] examined the prostate cancer mortality in each follow-up year, thereby allowing both the timing and extent of the reduction to become clear. In addition to the use of moving averages, a formal curve-fitting approach was used to further reduce statistical noise, to objectively measure the

steady state reduction in mortality, and to identify when it reached this level. WebFigure 4(b) shows the yearly numbers of prostate cancer deaths in each arm, along with the mortality rate ratios for the intervals centered on years 2, 3, … 12.

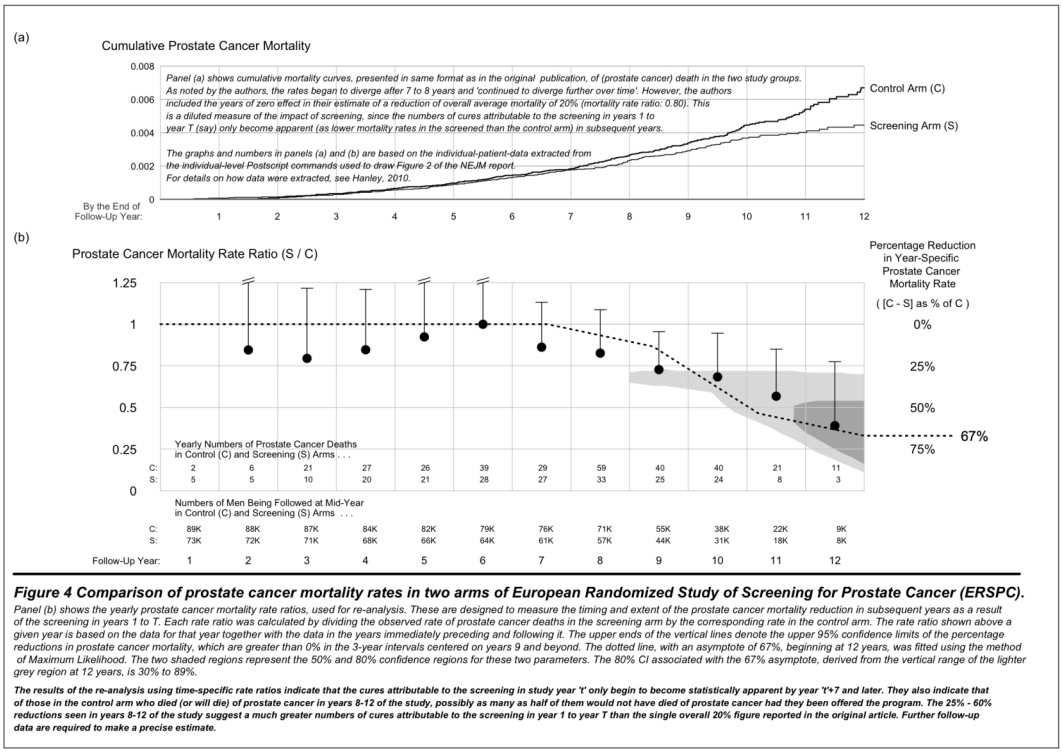


Figure 4 Comparison of prostate cancer mortality rates in two arms of European Randomized Study of Screening for Prostate Cancer (ERSPC).

Panel (b) shows the yearly prostate cancer mortality rate ratios, used for re-analysis. These are designed to measure the timing and extent of the prostate cancer mortality reduction in subsequent years as a result of the screening in years 1 to T. Each rate ratio was calculated by dividing the observed rate of prostate cancer deaths in the screening arm by the corresponding rate in the control arm. The rate ratio shown above a given year is based on the data for that year together with the data in the years immediately preceding and following it. The upper ends of the vertical lines denote the upper 95% confidence limits of the percentage reductions in prostate cancer mortality, which are greater than 0% in the 3-year intervals centered on years 9 and beyond. The dotted line, with an asymptote of 67%, beginning at 12 years, was fitted using the method of Maximum Likelihood. The two shaded regions represent the 50% and 80% confidence regions for these two parameters. The 80% CI associated with the 67% asymptote, derived from the vertical range of the lighter grey region at 12 years, is 30% to 89%.

The results of the re-analysis using time-specific rate ratios indicate that the cures attributable to the screening in study year 't' only begin to become statistically apparent by year 't'+7 and later. They also indicate that of those in the control arm who died (or will die) of prostate cancer in years 8-12 of the study, possibly as many as half of them would not have died of prostate cancer had they been offered the program. The 25% - 60% reductions seen in years 8-12 of the study suggest a much greater numbers of cures attributable to the screening in year 1 to year T than the single overall 20% figure reported in the original article. Further follow-up data are required to make a precise estimate.

After an expected delay (which the data indicate is approximately 7 years), the prostate mortality reductions that become evident in years 9 and beyond are statistically significant and considerably greater than the reported 20% reduction. It was not clear whether the steady state reduction has yet been reached, as the numbers of deaths are not sufficient to precisely measure the signal in the very follow-up time-window where it is probably strongest (follow-up ended in Dec. 2006, just as the pattern began to emerge).

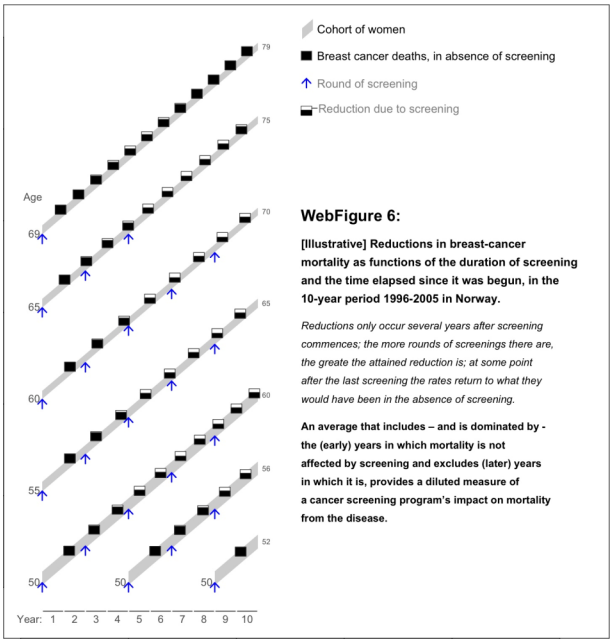
The re-analysis respects the intention to treat principle, using time-specific rates to reveal the expected non-proportional hazards pattern. The objective curve-fitting approach avoids having to "pre-specify" when the reduction reaches steady state; it specifies the smooth form of the rate-ratio curve, but allows the *data* to inform us about the two essential parameters: the timing and extent of the cancer mortality reduction enabled by screening.

By *entirely* ignoring the frequency and duration of screening, and the *location of the prostate cancer deaths in the time domain*, a meta-analysis[10] of the 6 RCTs of screening for prostate cancer (largely overlapping those in WebTable 1) compounded the conflation (see 2011 review).

1.5.2 Past screening trials: Breast cancer

Our review (appendix) also found major problems with analysis of RCTs in this area. In addition, the last decade has seen a number of reports based on data from organized Population-based Screening Programs ("service" screening). Notable examples are those from Copenhagen[11], England[12], Norway[13], and Sweden[14]. Sadly, here again, in every instance, these reports have been insensitive to the timing (in calendar-time and in age) of the mortality reductions that follow. In every instance, the reductions that would prevail in a steady state have been under-estimated.

The most recent example of this failure to properly deal with the 2 critical dimensions of the Lexis diagram is illustrated opposite. In lieu of new *RCT* data, we expect to see more of this type of analysis of *population* data, and it is important that the issue of the principle of time-specificity (in both screening time and age) be fully understood and put into practice using appropriate data-analysis methods.



WebFigure 6:

[Illustrative] Reductions in breast-cancer mortality as functions of the duration of screening and the time elapsed since it was begun, in the 10-year period 1996-2005 in Norway.

Reductions only occur several years after screening commences; the more rounds of screenings there are, the greate the attained reduction is; at some point after the last screening the rates return to what they would have been in the absence of screening.

An average that includes – and is dominated by - the (early) years in which mortality is not affected by screening and excludes (later) years in which it is, provides a diluted measure of a cancer screening program's impact on mortality from the disease.

Even though breast cancer is the last of the 4 cancers we will look at [after we are able to show data-holders results of objectives (1) and (2), and persuade them to share], *we include this schematic diagram (only some cells shown) to help explain our data-analysis model.*

1.5.3 Past screening trials: Colorectal cancer

The main message from our review[5] of the 4 large RCTs of Fecal Occult Blood (FOB) testing was again one of considerable under-estimation. In the worst of the 4, we liken the mis-leading analysis to the misleading answer to the question "how much would *regular sustained use of statins* reduce ones LDL cholesterol?". Imagine that the answer, "an average by 5%", was based on 16 serial (monthly) LDL measurements but ignored the fact that data are based on just 2 months of use and a further 14 of non-use. To take the analogy further, the reporting of say a 15% reduction in cholesterol because that was the first reduction, in a series of interim analyses, based on serial weekly data, in which the average (*over all on-statin measurements up to then*) showed a statistically significant reduction relative to pre-statin measurements.

The report[15] on the once-only flexible sigmoidoscopy trial is the first we have seen (since the 2002 re-analysis of the Malmo mammography data) to deal with time-specificity of incidence rate ratios; but mortality rates (and ratios) were still conflated, both anatomically and temporally.

1.5.4 Past screening trials: Lung cancer:

Our review of the 2000 report of the Mayo Lung Project[3](chest x-ray & sputum cytology) notes that it indiscriminately pooled *all* lung cancer deaths, from those in year *1 (before any impact could become evident)* to *24 (18 years after, and thus along after any possible impact of, the last screen).*

The National Lung Screening Trial (NLST)[16] enrolled and offered smokers 3 annual screens with low-dose helical CT or standard chest X-ray. The stated primary scientific goal: "to determine *whether* [italics ours] three annual screenings with low-dose helical computerized tomography (LDCT) reduces [sic] mortality from lung cancer" is typical of the " 'zero versus non-zero reduction" p-value-based decision making that drives most clinical trials. However, as we repeatedly stress, this paradigm has very different consequences for cancer screening trials than it does for trials where a virtually immediate reduction is expected or where the greater reductions are at the front (proximal to randomization) end of the time scale than the back (distal) end. The Nov. 2010 announcements[17] of the stopping of the trial (and informing the participants, since "the primary scientific goal of the NLST had been achieved") stated that "screening of people at high-risk for lung cancer with low dose CT *significantly reduces* lung cancer death" The NCI(US) stated that "an interim analysis of the study's primary endpoint, reported to the DSMB on Oct. 20, 2010, revealed a *deficit of lung cancer deaths in the CT arm, and the deficit exceeded that expected by chance*, even allowing for the multiple analyses conducted during the course

of the trial. Data presented at previous DSMB meetings did not meet the requirements for statistical significance with respect to the primary endpoint." Over the average of ~6 years (inferred range about 5 to 8) the `deficit' was 442 – 354 = 88 lung cancer deaths [a 20% reduction].

Funders would now very much like to know "in steady state, in a population of current and ex-smokers aged 55-85, in which CT screening is offered say annually or biennially from ages 55 to 75, how many lung cancer deaths would be averted each year? This is a very different question than the none/some existential question that drove the design and analysis of the NLST; the answer rests exquisitely on the timing of the deficit of 88 deaths in the NLST. For now, all we have to go on is the 20% reduction. Suppose (hypothetically, but not entirely unrealistically) that the numbers of lung cancer deaths in years 1 to 8 are 10, 38, 65, 75, 82, 90, 60, and 22 (total 442). Suppose also (again hypothetically, but not unrealistically) that the corresponding numbers in the CT arm are 10, 36, 59, 59, 56, 63, 50 and 21 (total 354), yielding yearly deficits of 0, -2, -6, -16, -26, -27, -10, -1 (total: -88). These deficits would translate into yearly percent reductions of

year:	1	2	3	4	5	6	7	8	Average
	0%	5%	9%	21%	**32%**	**30%**	17%	5%	20%

If this is the case, then we would expect that in the steady state, there would be sustained reductions of ***at least 30%*** *each year for ages 60 to 80 as a result of screening when people were 55-75*. In a true (service) screening program, the impact of the first [prevalence] screen would be smaller in absolute numbers and different than it was in the NLST, and the impact of *each* new [incidence] screen might be more concentrated (and the deficit deeper) L years later (L =Lag = 3-4 y ?) than it was in the NLST. We do not have the yearly deficit data at this time, but the *20%* in and of itself is not sufficient, since the reductions must be a strong function of year.

Funders are less interested in whether the cumulative impact of an *arbitrary* number (3) of screens (of a specific *spacing*) chosen for a research study was statistically significantly different from zero at some point. Needed instead (as its drives the sustained long term effect of *any* regimen) is *the impact of 1 round of screening*, *repeated say 20 times over say a 20 year age span from say A to A+20*. Say we knew that *1 round of CT screening at age t produces deficits of 5% 15% 25% 15% and 5% in years t+2, t+3, t+4, t+5 and t+6*. Then we could (with some very reasonable assumptions) calculate for repeated screenings (boluses) spaced 1.5 (or 0.5, or 1, or 2) years apart, what the sustained reduction (from age A + 4 to age A + 24, with a few years' 'shoulder' on each end) would be from the accumulation of all such (past) screenings.

1.5.5 Summary of data-analysis deficiencies in past screening trials

The 20% reduction reported from the NLST is identical to that reported from the ERSPC (which was also stopped when the P-value crossed the preset p=0.05 boundary). Had there been interim analyses of the UK sigmoidoscopy trial, and the same stopping boundary employed, it too would have been stopped at a reduction of 20% rather than the 31% reduction that had built up by the time the data were actually examined. This is not a benign coincidence; rather it is stark warning that in cancer screening studies, with their delayed reductions in mortality, prevailing data-analysis methods and stopping rules lead to underestimates. If in a cancer screening trial, one also uses *all deaths* from time screening commences, the first percentage reduction which was statistically different from zero will underestimate the asymptote that, in a population aged A to A+30, screened from A to A+20 say, would prevail from say age A + 4 to age A + 24. This asymptote is indeed the ultimate 'parameter' of interest to payers. Since mortality reductions from cancer screening manifest distally, enrolling and following more people for short length of time is *not* a more precise shortcut to an *unbiased* estimate, but to an *under*estimate: unlike in the more common virtually instant reductions seen elsewhere, the units of person time in cancer screening studies are not 'exchangeable in time'. The only way to estimate the asymptote in an unbiased (and practical) way is via the convolution (summing) of past impacts that we sketched above, and will describe more fully in the plans below.

1.6 Currently available sample size planning tools and data analysis models

After the 2010 press release, we communicated with the NLST biostatisticians that we hoped the analyses to be included in the full report would pay particular attention to the timing of the deaths. They replied that the design and analysis approaches were addressed in the article "The National Lung Screening Trial: Overview and Study Design".[16] The sample size and *timing-of-analysis* planning described there relies heavily on a very technical and very elegant paper by Hu and Zelen[18]. But, their method depends on a very large number of 'inputs', some not readily or reliably estimated. Second, and more importantly, whereas the methods use the same idea we will (the repletion of many rounds of the same screening regimen), in the end the analysis statistic simply involves just the number of deaths over the entire period of follow-up. Thus while it may answer the question: cumulatively, up to the time of the analysis (and the selection of that time is critical), would 3 rounds of screening show a definite (definitely non zero, in the statistically significant sense) reduction in lung cancer deaths. The 3 rounds and the associated duration of follow-up are arbitrary, and the reduction which is statistically significant at that time is an underestimate and does not answer the question as to long-term reductions with long term service screening. Our statistical approach improves in 2 ways on the Hu & Zelen approach: for sample size *planning*, the inputs will be much simpler and easier to find. And *more importantly,* unlike in theirs, the time-specificity and *parameters* are also used in and extracted directly from our *analysis*.

1.7 Sharing the information about the parameters without sharing the raw data

We will be asking data-holders from the various trials for the information to fit the parameters of our model. Even though we do not require individual level data, some may be reluctant to disclose even the count data (see below) that are needed. However, we can meet their concerns by using likelihood techniques. If we wish, e.g., to estimate the (3-dimensional) parameter $\boldsymbol{\theta}$ describing the future impact of 1 round of screening by joining the ERSPC information from a sub segment where screens were 2 years apart (Sweden) from others where it was say 4, all we need is to add the separate log-likelihoods [LogLik($\boldsymbol{\theta}$)'s] from the different sub-segments. Based on the code we will supply to the data-holder to calculate their LogLik($\boldsymbol{\theta}$,design,data) contribution, that data-holder can supply us with their LogLik($\boldsymbol{\theta}$) contribution without disclosing the outcome data that went into the calculation (we will have already mutually established the rows of their design matrix (see below). A 2003 NSF RFA[19] called for development of methods that promote data sharing, but we have not found documented examples of this strategy. It should add to the prospects of collaboration (cf. correspondence).

2 OBJECTIVES

The *broader and ultimate objective* is to enable planners to use 3 core parameters describing the impact of 1 round of screening to project the effect (in terms of steady state mortality reductions) achievable in the future, if a specified regimen of screening (not necessarily the one used in past trials) were started to today. It would also allow them to quantify what is currently being achieved using a program that has already in operation for some time.

We emphatically distinguish three separate aspects that often tend to be uncritically mixed together:

(a) the 3 core parameters (theoretical) that characterize the impact of 1 round of screening, and that can be repeatedly 'chained' for projections for service screening

(b) the structure of, and reported cumulative results in past trials. Each of these employed a specific arbitrary finite numbers of rounds of screening; we will use them to estimate the parameters in (a); we will *not* use them to test whether or not (as was done in the NLST) that specific number of screenings -- 3 in the NLST -- has a cumulative non-zero effect on mortality over some stopping-rule-determined period of follow-up (6 years, range 5-8) ; and

(c) the steady state reductions that would be produced by "service" screening (not necessarily with same spacing used in any completed trial) between 2 age limits in a dynamic population, and that we illustrated in WebFigure 2 above. The parameter values in (a), along with the spacing and anticipated participation rates, are what determine (c).

Our immediate *objective* is to develop a way to statistically estimate these 3 parameters in (a) from age-, follow-up-time- and study-specific mortality data, either from conducted screening trials, or from population data. Thus, the *detailed objective*s are to

(1) develop, refine and test a statistical method to estimate the 3 core parameters using data from a single screening trial that used a single regimen

(2) extend this method to handle data from a single screening trial with different screening frequencies (e.g., FOB tests annually and biennially in some colon trials, PSA tests biennially and quadrennially in the ERSPC) or from several screening trials of the same technology/techniques, with different screening frequencies or ages, different durations, different participation rates, and different amounts of follow-up.

(3) offer guidelines on how much data are needed (within one trial, or from the combined data provided by several studies of the same technology/technique) to statistically estimate, with a desired degree of precision, the 3 core parameters, and more importantly the steady state reduction that could be achievable in a screening program with a specified design and

(4) apply these methods to fit core parameters estimates to the data from past trials and from populations where there are extensive existing data (for cancers of the prostate, colon, breast and lung).

3 PLAN

3.0 Overview/timeline: Year 1 will be devoted to objectives (1) and (2), year 2 to objectives (2) and (3), and to obtaining the necessary data for objective (4), and year 3 to applying the methods developed under (1) and (2) to these data, and to illustrating how the fitted parameter values can be used to make projections for cancer screening programs with different screening frequencies and age ranges.

3.1 Objective 1: The statistical method to be refined and tested borrows from the design matrix used in regression problems, and from the concept of the Lexis rectangle used in demography. Consider a single screening trial, with a k:1 randomization to screening or not, with entry ages in the range A (say 50) to A+19 (say 69), entry staggered in calendar time, a given spacing of a certain maximum number of rounds (say 4) of screening (not necessarily equally spaced, for but illustration assumed to be biennial), and a maximum amount of years follow-up, say 18, from when the first subjects entered the trial. This generates a region of $20 \times 18 + (1/2) \times 18 \times 17 = 513$ age-year follow-up cells in the Lexis space (the Lexis diagram in WebFigure 6, albeit with only 10 years of follow-up, should help with the visualization).

In cell (a,y) for persons who were age a, in year y, the ratio of the person-years in the arms would still be approximately k:1, and the numbers of deaths from the cancer in the screening (1) and non-screening (0) arms in this cell would be d_1 and d_0 (further subscripts suppressed).

The theoretical rate ratios (RRs) in the 513 different cells would vary from one to another. The rate ratio would be very close to 1 in those peripheral cells where the persons involved had had few previous screens (e.g., age 79, year 10; age 62 year 1; age 51, year 10) or -- even if they had had the opportunity of the maximum number of 4 screens -- it had been many years since the last screen (age 78, year 18, i.e., 12 years). The rate ratio would be furthest below the null in the central cells in the Lexis space (e.g. ages 58, 68, 78; year 8). The 'depth' or reduction below the null in these cells would also be a function of the total impact of each round of screening: the reduction would be considerable if each round resulted in the cure of many cancers that would otherwise have proven fatal within that cell; if it resulted in the cure of only a few otherwise fatal cancers, then the reduction in that cell would be smaller. The shape of the rate ratio function as it tracked along a diagonal of the Lexis space could also have some 'local' hills and valleys if the rounds of screening were spaced too far apart to maintain a sustained reduction.

The key feature in our model (also implicit in the sequential calculations used by Hu and Zelen) for the reductions in Lexis cell (a,y) is the accumulation of effects from each of the rounds of screening that persons in that cell were exposed to in earlier years along the same diagonal. Effects of different rounds

are assumed to be identical, except possibly for the first one. Thus, if we can specify the effect of a single round by a few interpretable parameters, and for every (a,y) cell know when and how many of these rounds had been applied, then we can calculate the reduction in that cell as a result of all of these previous screens. For example, in the cell where people are now 71 and in year 5, the rate ratio is determined by the reductions produced by the first screen at age 66, the second at age 68 and the third at age 70. It rate ratio would be smaller (the reductions would be deeper) in the (73,7) cell, since by this time this cohort would have had an additional fourth screen at age 72.

The mortality difference that one round of screening at a given time makes to 'future' cells is limited to the number of 'otherwise fatal' cancers within these cells along the relevant diagonal. The lag L from when an otherwise fatal cancer is screen-detected and cured until it would have otherwise proven fatal is considered a random variable, since it will differ across the persons involved. Our plan is to parameterize this distribution (and the fraction of persons involved) as simply as possible, by 3 numbers. The first of these is the mean or mode (μ) (measured in years and fractions thereof) until the maximal impact is expressed: The second is the spread (σ), a standard deviation type measure, also in years) of the distribution, and the third is the magnitude (γ) of the reduction (as say a percentage of all of the cancers that would otherwise have proved fatal in that year) over the year where the maximal impact is expressed (see Fig 1 in 2005 Epidemiology paper). We think of these 3 parameters as specifying how *deep* and how *wide*, and *how far into the future* the (delayed) is the mortality deficit produced by this 1 round. Other equivalent parameterizations will also be considered. In the (a, y) Lexis rectangle defined by a 1 year of age and 1 calendar year, the fraction, f, of the deaths from cancers that would have otherwise proved fatal in that cell, but were in fact averted by that single round of screening t years ago, is a function of t, μ, σ, and γ, and so we denote it by $f(t, \mu, \sigma, \gamma)$. It can be calculated by integrating over the appropriate 1-year window of the distribution. Note the *'backwards from the death to the screening*' time direction, the same one followed by 'case-control' epidemiologists who use non-experimental (ie non-rct) approach. If (as in our example above) there had not 1, but been 3 previous screens, t, t-2, and t-4 years ago, the fraction of the otherwise fatal cancers that would have proved fatal in that cell that was in fact prevented by these *3 screens* is given by the fraction F_{averted}, where F_{averted} is linked to f by the following expression

$$F_{\text{averted}}(\boldsymbol{t},\boldsymbol{\theta}) = f(t,\boldsymbol{\theta}) + [1-f(t,\boldsymbol{\theta})] \times f(t-2,\boldsymbol{\theta}) + [1-f(t,\boldsymbol{\theta})] \times [1-f(t-2,\boldsymbol{\theta})] \times f(t-4,\boldsymbol{\theta}),$$

and where $\boldsymbol{\theta}$ is shorthand for the vector of 3 parameters μ, σ, and γ, and bold $\boldsymbol{t}$ is shorthand for the collection of the locations back in time (t, t-2, t-4) of the three screens, relative to the time that defines cell (a, y). Denote the complement of $F_{\text{averted}}(\boldsymbol{t},\boldsymbol{\theta})$ by $F_{\text{despite}}(\boldsymbol{t},\boldsymbol{\theta})$. It is the fraction of the 'otherwise fatal' cancers in that cell that still prove fatal despite screening. If we fix or condition on the total d of the numbers of deaths d_1 and d_0 in the cell, the expected split of $d_1 : d_0$ is $[k \times F_{\text{despite}}(\boldsymbol{t},\boldsymbol{\theta})]$:1 so $(d_1 \mid d) \sim \text{Binomial}(d,\pi)$, where $\pi = [k \times F_{\text{despite}}(\boldsymbol{t},\boldsymbol{\theta})] / \{[k \times F_{\text{despite}}(\boldsymbol{t},\boldsymbol{\theta})]+1\}$, and $\text{logit}(\pi) = \log(k) + \log[F_{\text{despite}}(\boldsymbol{t},\boldsymbol{\theta})]$. Thus the binomial-based log-likelihood contribution from cell (a,y) is a function of the random variables d_1 and d_0, the parameters $\boldsymbol{\theta}$ in $F_{\text{averted}}(\boldsymbol{t},\boldsymbol{\theta})$, and the 'design' or 'timing of previous screens' vector $\boldsymbol{t}$. Each row of the design matrix gives the vector $\boldsymbol{t}$ for the cell in question, and the numbers of deaths can be stored as 2 columns, 1 row per cell. The overall log-likelihood (LL) is the sum of the contributions from all of the cells that have at least 1 cancer death, and since d_1, d_0, $\boldsymbol{t}$ and k are given for each cell, the LogLikelihood is a function of the 3 unknown parameters in $\boldsymbol{\theta}$. It can be maximized either numerically or analytically, depending on how the distribution of L is specified, and the inverse of the curvature matrix at the MLE used as a variance matrix for the ML estimate of $\boldsymbol{\theta}$. The likelihood can also be modified to reflect (using an offset) the less than 100% participation in the screening arm, and more than 0% screening in the non-screening arm, so that one can estimate $\boldsymbol{\theta}$ in an ideal 100:0 situation (this would allow planners to project what would happen with participation rates that were higher or lower than those in an actual trial.

The feasibility, accuracy and performance of this fitting approach will be tested extensively in

simulated (but realistic) data situations that reflect the actual screening schedules and samples sizes. The implications of different amounts of follow-up time as well as numbers and timing of deaths in relation to the timing of screening will be closely examined and documented.

3.2 Objective (2) Because of how it is conceptualized, a round of screening should have the same impact no matter when it is followed by the next round. Thus, for example it is straightforward to accommodate data from ERSPC segments where screening was biennial and quadrennial, there were different durations of screening, in ERSPC segments where the randomizations differed (1:1, and approximately 5:6), ages were slightly different, participation rates differed, as did amounts of follow-up. One simply splits each (a,y) cell into segments, and specifies these variations in the relevant rows of the larger design matrix. The information is again combined by adding the LogLikelihoods which remain functions of $\boldsymbol{\theta}$. The same approach can be extended to combine the information from different studies, but we stress that we will not merge studies unless the basic screening *technique* is common.

3.3 Objective (3) Whereas it appears *we* are interested in $\boldsymbol{\theta}$**,** planners are interested in combining them with a new and much longer-in-time design vector spanning 30 years from say 50 to 80, and 10 screens from age 50 to 70 say, and estimating the steady state reductions over the 30 year age-span. This is analogous to the use of n observations to fit the β coefficients in a multiple regression, and the applying these to a new vector of explanatory or design variables x, and asking how precise this 'prediction' is. We will study how estimation errors are compounded, and whether it is critical to be able to precisely estimate both σ and γ or whether it is some combination of them that matters. Thus, we will also investigate the sample size requirements needed for the planners' estimates (made by combining a new $\boldsymbol{t}$ -- and possibly different participation rates -- with the estimated $\boldsymbol{\theta}$**)** to achieve a desired precision. In (1) and (2) we will also use s a backup a direct sigmoid rate ratio curve such as we did in the ERSPC re-analysis.

3.4 Objective (4) In order to estimate $\boldsymbol{\theta}$ using real data, we will need the (d_1,d_0) pairs in each (a,y) cell in each study, or sub-segment of the same study, along with the corresponding $\boldsymbol{t}$ vectors, and randomization ratios.

We plan to begin using the data from the 5 **prostate** cancer trials, and then proceed to colon and (lastly) breast. Professors Schröder (entire ERSPC, the one of the 5 trials in prostate cancer screening with the greatest resolving power) and Hugosson (Swedish component of ERSPC prostate trial with every 2 years rather than every 4 years screening) are favourable to this initiative and have offered us their support (cf. e-mails). Despite the fact that our J Med Screening article was somewhat critical of the ERSPC analyses, we shared all of our work with Professor Schröder right from the beginning and he is keen to see an even finer re-analysis that uses both age and screening year, and more follow-up data in the very years where the signal should ultimately be the strongest. Last year he invited the principal applicant(JH) to be a formal collaborator in their work, but JH declined at that point as he did not want his involvement to be seen as a way to make the ERSPC statisticians and epidemiologists on that 20 year team feel like they were being coerced into changing how they (and their peers in other cancer screening studies) do their data analysis. Now that our initiative is couched in even broader terms, and will involve all 5 studies, it should be less threatening. At the time we wrote to him in early February, we had not yet thought of the 'sharing of log-likelihoods' approach that we have just now offered to Dr Church (colon).

Dr Church is keen to collaborate on the FOB screening studies in **colon** cancer (see letter) and he has access not just to the Minnesota FOB trial data, but to 2 European FOB studies as well.

Dr Mandel, whom we initially approached, suggested that we enlist Dr Robert Smith of the ACS as he has worldwide contacts in screening and has published with many of them. JH has already met and participated with Dr Smith in a panel at a meeting on lung cancer screening where a similar data-pooling project was being discussed. We particularly wish to take advantage of his political and scientific connections in our data-extraction efforts to do with **breast** cancer, as this is by far the most polarized and fractious. We do not want to polarize it further, or take sides, but we feel we have a strong case to

make for a new way to deal with cancer screening data is also why we are leaving breast cancer to the last years, as it will take the greatest amount of delicate negotiations regarding data-sharing. We will of course emphasize that we do not even need the Lexis counts, and that likelihood-function sharing is sufficient. We do not want to jeopardize our prospects at this early stage. The one breast cancer PI we did approach wondered why we needed to re-do everything, and added: "Canadian breast cancer screening trials cannot be lumped together with the population-based randomized trials; they were not population-based, they had a pre-screening palpation involved and that is only a fraction of the differences." We responded that we had no intention of blindly merging trials.) But before approaching others in the highly charged and polarized breast cancer area, we will wait until we have theoretical results from objectives 1 and 2, and concrete ones from the colon trials. At that time, we will also had more experience with the 'sharing the log-likelihood function' approach, and we will, just in case, also enlist Dr Smith's support at that time.

4 ROLES AND SKILLS OF MEMBERS OF RESEARCH TEAM

Prof. **Nandini Dendukuri** is a biostatistician who works extensively in heath technology assessment, and is an expert in Bayesian methods, which we will need for parameterizing and fitting the models (our use of Bayesian models is less because of a desire to impose strong priors on parameters, and more about the attractiveness of the methods in parameter fitting, especially when the models do not fit within the usual generalized linear models framework; however, we will use priors to impose realistic constraints and boundaries on some of the time parameters. She has published articles on methods for the evaluation of diagnostic tests in the absence of a gold standard, for correction of verification bias in the absence of a gold standard test, correction of verification bias in a meta-analysis setting, and for designing diagnostic studies in the absence of a gold-standard reference test. She has also developed a number of free, user-friendly software packages that have made sophisticated statistical methods such as latent class models and hierarchical models more accessible (http://www.nandinidendukuri.com).

Prof. **Erin Strumpf** is a health economist. Her research in health economics focuses on the impact of health care system policies on spending and health outcomes overall, and in disparities across groups. In current work, she is evaluating the costs and benefits of population-based cancer screening policies based on U.S. and Canadian guidelines.[20] [21] [22] These analyses use nationally-representative survey data and administrative data from cancer registries and vital statistics in both countries. She will be active in the research design and data analysis for the proposed research. Her experience communicating research findings to policymakers will also aide in the diffusion and application of the output.

PhD student **Zhihui (Amy) Liu** is a biostatistics student under our direction; she gained experience with WnBUGS software and mixture models (we will use similar ideas when fitting convolutions of screening rounds) during her Master's training at McMaster University. She will, under our direction, and as part of her dissertation work, be responsible for developing, implement and testing the fitting of the statistical model described above (objectives 1-3).

The **RA** will be responsible for data acquisition for objective 4, and general research tasks.

Prof. **James Hanley** is an experienced and internationally recognized biostatistician. He has had a long interest in cancer, starting with his involvement in cancer clinical trials (with M Zelen) in the ECOG and the RTOG in the 1970s; His roc work with radiologist McNeil is widely cited; he introduced it to other biostatisticians who have further refined and extended it. He spent a sabbatical year at the Cancer Unit of WHO in Geneva in 1985-86 and published in their Bulletin on the statistical evaluation of prevention programs in cancer. His 1998 and 2005 JAMA articles with Connecticut Urologist Albertsen on the natural history of untreated prostate cancer, and his 3-ply Kaplan-Meier-type curves showing competing risks, are highly valued by physician and patients. He co-authored, with McGregor and others, a report to the Québec Ministry of Health in the mid 1990s on whether it should pay for PSA tests; he has written

3 papers on the appropriate way to analyze data from cancer screening trials: the 2005 one[2] showed the benefits of time-specificity, and how it can recover 'signals' and 'hiatuses' hidden in cumulative mortality rates. Fig 1 in that article illustrates the 'convolution' technique we plan to exploit in the proposed work. His 2010 J Medical Screening article (re-analysis of ERSPC) shows more clearly, and quantifies, the timing and extent of the reductions in prostate cancer mortality produced by PSA screening, and established his relationship with Dr Schröder. The curve fitting used in that article will serve as a point of departure from the proposed work in the present application. His 2011 Epidemiologic Reviews article documented the inadequacies of the prevailing data-analysis techniques applied to cancer screening data, and the findings in that review are what prompted the current application for funding. He has organized a symposium, sponsored by the Canadian Society for Epidemiology and Biostatistics, at the upcoming Epidemiology Congress in Montreal on the under-use of the data from, and the underestimation of the mortality reductions produced by the screening in, RCTs of cancer screening.

5 SIGNIFICANCE

Most provinces have organized screening programs for cancer. As best we know, all have programs for breast cancer. Ontario has one for colorectal cancer and some other provinces have programs under development (Appendix). Those attempting to justify a program for a specific cancer are hampered by the type of information available from, and the p-value-driven stopping rules used in, reports of RCTs of screening. The analyses of population data have shown similar time-insensitivities.

The most recent NLST is a cogent case in point. We do not know whether Canada's provinces consider themselves rich enough to begin offering regular spiral CT of smokers for lung cancer. Nor do we know whether the persons in these provinces with a large number of pack years of smoking are willing to undergo the scans. There will be some collateral harm from the radiation exposure. And one can expect considerable anxiety for a fraction of those scanned initially (a much higher fraction than with an initial mammogram) in whom some abnormality is seen on that prevalence scan: they will have to return is say 3 months to undergo a high dose scan to decide whether the change (or lack of it) in the size of the suspicious lesion is (in most instances) a false alarm or (in a few) evidence of an actual lung cancer that will require substantial surgery. But we do know (McNeil, personal communication 2011.02.27) that Blue Cross (USA) is currently considering the question, presumably on the basis of the results that prompted the 'stopping' of the NLST (screening stopped at the end of year 2) and the release of the statistically significant 20% reduction a few months ago.

Our review suggests that even when the full NLST results are published, they will be of the same form as those in all of the previous cancer screening trials, and thus not very helpful for planners. Our proposal seeks to break this cycle. *We will distinguish the answers planners need from questions trialists tend to ask.* The planners wish to know about a program (possibly with a different spacing that has been studied) that continues each year, within a specified age range, and with effects that extend well beyond that range. The trialists tend to ask more yes/no-type questions, concerning a somewhat arbitrarily selected and protracted, and possibly research-funding-dictated, screening schedule, and with results cumulated over a number of follow-up years, that number to be decided by a p-value and a DSMB.[23]

Our aim is to use the data from these trials (even though they were not explicitly designed to provide estimates of the parameters we seek, and would have been designed very differently, if the study were to pursue the core parameters) to estimate the parameters the planners need for their cost and (especially) benefit calculations. Since the trials, even when carefully combined, may not allow sufficiently precise estimates of the core parameters, we will supplement them with data, analyzed with a focus on the same core parameters, from populations where "service" screening programs have been introduced sufficiently long ago to now show their (delayed) effects. Thus, we aim to fill an important information gap for health policy decision-makers and program planners, and to show statisticians and epidemiologists how to plan, and generate such information from, new RCTs, and obtain similar information from other data sources.

Appendices to proposal of Hanley, Dendukuri, Strumpf and Liu.

1. References

2. Letters of Support

3. Links to information on provincial screening programs

4. Full versions of 2005, 2010 and 2011 papers by JH on screening, along with draft of a paper, targeted at scientists at large, on need for time-specificity, departure from a proportional hazards model, and more careful use of interim analyses, when analyzing data from cancer screening studies

References *(Those preceded by an * are included in the appendix)*

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LETTERS OF SUPPORT

Re: seeking your support for a data project
Jonas Hugosson [jonas@urol.se]

Sent:
February 6, 2011 11:17 AM
To:
James Hanley, Dr.; secr.schroder@erasmusmc.nl;
laszlo@mammographyed.com;
kansliM@kansliM.lu.se; jack.mandel@utoronto.ca; w.atkin@imperial.ac.uk

Cc:
Nandini Dendukuri, Dr.; Erin Strumpf, Prof.; Zhihui Liu; James Hanley, Dr.

Dear Dr Hanley
I have a positive attitude to this co-operation. As far as I understand your method is interesting and will compensate for the fact that individuals entering a randomised screening trial do that in various age group and not from a certain age as will be the case in population-based screening-program. At this point I understand you just need this message for going on with the aplication procedure. One criticism from me is that you try to involve all cancer screening trials which might be a bit too much to start with, I guess it would be best to start with one cancer (breast or **prostate**) and then proceede with others later.
Best luck

Jonas Hugosson

February 8, 2011 7:47 AM

Dear Dr. Hanley,

Thank you for your mail of February 5, 2011. I am delighted that you engage on a major project using data-reconstruction in evaluation of randomized screening trials. I remain very much impressed by the work I have seen so far.

As the international coordinator of the **ERSPC** study group, I promise that I will discuss your proposal in a very promoting way. I know that the readiness to cooperate with you is there, and it will all depend on conditions to
be worked out.

It would be important to have a very specific request; specifying the information you wish to obtain from ERSPC. With that in hand I could make concrete proposals at our next ERSPC group meeting, which will take place from April 14-15, 2011.

I am looking forward to your reply.

With best regards,

Prof.dr. F.H. **Schröder**
Coordinator ERSPC

jack.**mandel**@utoronto.ca [jack.mandel@utoronto.ca]

February 9, 2011 11:50 AM

You forwarded this message on 2011-02-19 11:31 AM.

An interesting project. I suggest you contact Tim Church at the University of Minnesota. Recently he directed an effort to combine the data from the 3 large RCTs of **fecal occult blood testin**g (Minnesota, Funen and Nottingham). When I left Minnesota I turned over the data to him. Tim is also involved in the PLCO trial.

I would also suggest you contact Robert Smith from the American Cancer Society in Atlanta who has been very involved in developing the cancer screening policy in the US and who is well versed on all the trials. He is very well connected in the cancer screening field throughout the world.

Good luck with the project. Let me know if there is anything I can do to help

Feb 18, 2011

Jim,

This is an intriguing idea, and I congratulate you on your inventiveness. Of course, the data could be back-calculated, but at some point we have to depend on each others integrity in this field.

I want to point out an essential difference in our FOBT data relative to the breast cancer data. The annual and biennial groups are randomly allocated, whereas intervention groups across breast cancer screening trials are not exchangeable. Exchangeability no confounding in comparing FOBT schedules, so adjustment is not necessary.

In any event, I will shortly send you a letter of support indicating that we would be happy to collaborate in reanalyzing the Minnesota FOBT data and would continue to explore with the relevant investigators the possibility of sharing the UK and Danish data as well. I hope this will serve your needs in the short run.

Regards,

Tim

Feb 28, 2011

Dear Dr. Hanley,

My study team and I would be happy to collaborate in reanalyzing the Minnesota **FOBT data** by adapting your analysis approach to the differences in screening schedule. The model would need accommodate the confounding of screening effect , compliance, and outcomes (which affect both mortality and incidence), but I am confident this could be accomplished.

We currently also have access to the UK and Danish data as well. I would be willing to continue to explore the possibility of sharing those data with the collaboration of the relevant investigators (currently Dr. Moss and Dr. Kronborg).

Sincerely,

Timothy R. Church, PhD
Professor, Environmental Health Sciences
University of Minnesota School of Public Health
Minneapolis, MN

On 2/28/2011 8:12 AM, James Hanley, Dr. wrote:
> Dear Dr Church
>
> I came up with a new idea since we communicated that should make it easier
> for data-holders to share the info. relative to the parameters we are interested in
> without disclosing their raw (or even count) data
>
> if we supply an R function to each data-holder, and ask them to fill in the
> deaths in the Lexis rectangles (we would know the design matrix) and let them
> run the R code and send us back the 3-d log likelihood
>   logLik(parameter1, parameter2, parameter3) over a 3d grid of
> parameter values,
> where these are the 3 parameters WE are interested in, then we can join
> the logLiks from different studies, or sub portions of the data (eg sweden with 2
> year spacing, others with 4 years apart) we would have what we puruse and they would
not have
> disclosed or 'sent overseas' their year-and age-specific death counts.. so win win !
>
> same would apply to annual vs biennial in fob screening, or different schedules
> and lengths of screening in 8 breast ca. screenings of women> 50
>
> I haven't seen this strategy used anywhere but would be delighted to try it out
> and so i will put this proposal in our grant application.
>
> Jim Hanley
>
>
>
> _____
> From: Timothy R. Church [trc@cccs.umn.edu]
> Sent: February 25, 2011 6:04 PM
> To: James Hanley, Dr.
> Subject: Re: FW: seeking your support for a data project
>
> Dr. Hanley,
>
> Your proposal sounds intriguing. I've actually played around a little
> with this idea myself. It quickly gets complicated, but I currently

have
> a PhD student developing a tractable (I hope) model for screening
that
> would play nicely in this realm with minimal augmentation. Right now
it
> only addresses incidence, but extending it to mortality would be
> straightforward. It uses maximum likelihood for estimation and can be
> run with discrete or continuous data.
>
> If you have ideas about funding, I would be interested in hearing
them.
>
> Regards,
>
> Tim Church
>
> On 2/19/2011 10:31 AM, James Hanley, Dr. wrote:
>> Dear Dr Church
>>
>> Jack Mandel suggested I contact you re a data-reconstruction project
I am
>> proposing to our Canadian Institutes of Health Research (see below)
>>
>> Instead of analyzing each screening study separately, I am
suggesting that with a simple statistical model
>> (see below) we can -- using a design matrix -- estimate the effect
of each round of screening and thus
>> be able to estimate 3 parameters than can be put together to project
what the effect would be
>> of any schedule of screening .. this approach would allow us to use
data from studies with different
>> screening schedules and durations towards one common goal.. and
that goal would not be to get a stronger p=-value
>> but rather an estimate of what each round of screening does by way
of reducing mortality down the line
>> (Its easy to put together the convolution if we know how many rounds
and the spacing)
>>
>> To do so we would need for each arm in each study, the numbers of
cancer deaths at the level
>> of the age-year cell.. so like a Lexis diagram.. with age on y axis
and time since screening
>> began on x.
>>
>> I think the estimate will come out much bigger than the prevailing
analyses
>> (which use a prop. hazards model) give .. and it will allow us to
project what would
>> happen in real screening programs, not just the shorter trials.
>>
>> I estimate that IN STEADY STATE a pop'ln screening program that
screened people in a 20-year age window
>> from say A to A +20
>> would influence to various degrees the death rates in the (1/2) 30
* 30 = 450
>> age-year cells (I'm allowing the effect of a screen could be 'felt'
as far away (in future) as 10 years
>>

>> Thus in a trial that screened ages A to A +20 for say 12 years
>> we would need the cell-specific counts of deaths in the 2 arms for each of the
>> (1/2) x (20+10) ages x (12+10) years = 330 cells
>>
>> (many would be zeros but collectively they would allow us to join them using the design matrix
>> with others from other similar studies..
>>
>> Given the smallish numbers of deaths in the cells where we would expect the largest impact,
>> every study added will be a bonus.
>>
>> I hope you will be able to give an initial positive response so we can get the funders
>> interested in this important project..
>>
>> Thanks
>>
>> Jim Hanley

===INITIAL (to all) e-mail of Feb 5 to some of the data-holders.====

Dear Prof. Hugosson (Sweden, Prostate)
jonas@urol.se

Dear Prof. Schroder (Rotterdam, ERSPC, Prostate)
secr.schroder@erasmusmc.nl

Dear Prof. Tabar (Sweden, Breast)
laszlo@mammographyed.com

Dear Prof. Andersson/Aspegren/Janzon (Sweden,Malmö; Breast)

This study was published before there were email addresses, and so i am asking kansliM@kansliM.lu.se at the faculty of Medicine to pass on this email to the authors of a ;pre-email' publication on the Malmö; breast cancer screening study

Dear Prof. Mandel (Canada (now), Colon -- Minnesota)
jack.mandel@utoronto.ca

Dear Prof. Atkin (UK , Colon)
w.atkin@imperial.ac.uk

Dear Professor

I am writing to ask if you would be willing to help out
in a 'data-reconstruction' project my colleagues and I
are embarking on.

I am not asking you to do (or enable) any work just now;
but I am hoping for a gesture that you would be willing to
help enable some work once our team has secured some funding.

[I am also asking if you would be willing to
make introductions for us to some of the other researchers
who have carried out the major RCTs in cancer screening,
especially in your country, or in the cancer you study.
And, since you yourself are one of them, we would of course
want to also contact you later in that capacity.]

We are asking this because we are applying this month to the
Canadian Institutes of Health Research for funds to
're-do' the data-analysis for the RCTs of screening
for cancers of the breast, prostate, colon and lung,
and to carefully combine the results for all of the studies
that employ the same screening for the same cancer.

****
If you don't have time now to read through our detailed plans,
you can skip to the second last section of this email,
marked " ** Here is our request for co-operation in the short term."
where I describe asking what I am asking for in the short term.

****

As you know, for much of the last 10 years we have been
advocating for time-specific analyses of the cancer

mortality rates in each arm in each trial. As we have recently documented in a review to be published in Epidemiological Reviews this summer,

(link :
text http://www.medicine.mcgill.ca/epidemiology/hanley/ForEpiReviewsFINALDec2010.pdf
Figs http://www.medicine.mcgill.ca/epidemiology/hanley/WebFigures.pdf
)

and as we have hinted at in papers we published in 2005 (colon) and 2010 (prostate), there has been widespread underestimation of the mortality reductions that followed the screening in the various trials over the last 3-4 decades.

Some of this has to do with the short screening regimens, some with the short follow-up (in the case of chest x-ray screening for lung cancer, they had too much follow-up.. well beyond what made biological sense, but obviously a poor test). But mostly the underestimation has arisen from not recognizing the delay between when a screen detects a (curable) cancer and when that -- if it were not screen-detected -- that cancer would have killed its host. The review goes on at some length to document how mis-aligned the cumulative mortality rates are with the biology in question.

One more feature has also contributed to the misleading estimates of the reductions that could be achieved with regular screening for say 20 years between say ages 50 and 70 (or whatever is relevant for the cancer in question). That is meta-analysis, where studies of all durations and screening intensities, and arbitrary follow-up, are merged together without any regard for time-specificity. Not surprisingly, (as is best evidenced by last summer's naive meta-analysis of the prostate cancer trials -- see our comments in the 2011 Review) these only serve to dilute and confuse even more.

And, lastly, this inattention to time-specificity is also being practiced widely in analyses of population data from entire countries that have introduced national screening programs. The 2011 review also comments on this and the misleading results some very eminent and influential authors published last fall in relation to breast cancer screening in Norway.

Our plan is to be doubly-time-specific. In our re-analysis of the ERSPC data, we used just 1 time-axis, namely time from 1st screen (or equivalent in control arm). But as you can see in the Review, in the diagram we drew to show what must have gone on in Norway, the numbers of deaths are critically 2-dimensional. the reductions in any one 2-D "cell" are a strong function of each of the two axes. Yes, there will be no reductions for x years after the 1st screen, but also, if a woman is screened just once, at age 69, the deaths rates 10 years later in her cohort are not the same as the death rates 10 years later in the cohort that was 1st screened at 59.. the latter cohort will have had the benefit of several screens since then.

Indeed, it is this 2-D grid of numerators (numbers of cancer deaths, by age and by no. of years since 1st and last screen) that is the key to our proposal, and we are setting out to reconstruct this grid of numerators for each of the 8 large trials in breast cancer (we will also pursue the studies that screen before age 50), prostate (5 or 6), colon (also 5-6) and lung. we are awaiting the publication of the stopped-in-Fall -2010 NLST lung trial with CT screening, with what was reported as a 20% reduction... again, sadly a meaningless number until we see where in follow-up time the deaths were located.. they screened yearly for 3 years, and there was about 5-6 years of follow-up.

Fortunately, from the descriptions of the studies, we think that the denominators (person years underlying the deaths in each 2-D cell) can be reconstructed without having to go back to the computer files. The relative sizes of the cell-specific denominators are all that matter for the statistical analysis, especially if they are not equal (as they would be in a 50:50 randomization).

So, we think the re-construction work boils down to obtaining,

for each arm in each trial...

the no. of prostate (or breast, or ..) cancer deaths in each calendar year in each age

so, for example, in screening arm..

..
2 deaths in year 1997 [year 7 in trial] at age 71
3 deaths in year 1998 [year 8 in trial] at age 72
..
0 deaths in year 1997 [year 6 in trial] at age 70
1 deaths in year 1998 [year 7 in trial] at age 71
..

And we think that our statistical model is a very plausible one.. its just like that shown in the Figure in our 2005 paper.

the screen at time t produces a 'deficit' of deaths

the CENTRE of the deficit is delayed at year t+D years, where D is the average DELAY (its the average time between when a cancer is screen-detected and when it would have OTHERWISE killed the host.)

[This average DELAY will have to be estimated from (fitted to) the available data.]

the SPREAD of the distribution of individual 'deficits' can be captured by a standard deviation, or other suitable measure.

[This degree of SPREAD will also have to be estimated from (fitted to) the available data.]

the DEPTH of the distribution of individual 'deficits' can be captured by a third parameter, which will also have to

be estimated from (fitted to) the available data.

If we KNEW the values of the 3 parameters in this model, we could predict what the EXPECTED numbers of deaths there would be in each of the 2-D cells described above.

Since we do not, we can reverse the thinking, and ESTIMATE the values of the 3 parameters in this model from the OBSERVED numbers of deaths there actually were in each of the 2-D cells described above.

That's the reason we need the data in more detail tahn is given in standard RCT reports.

The nice aspect of our proposed approach is that we can accommodate -- in ONE global data-analysis -- ALL of the data from all of the screening trials for a particular cancer.

This thinking is identical to what we do in multiple regression.. opposite from the 'y' (response) that was observed, we have a row of the features of the 'design' combination that produced that y. here our 'design matrix' will have for each 2-D cell in each arm in each trial, the location in time of that cell, i.e. it could be that it is the 10th year, and the person is now 68, and the (3) screens were 10, 8 and 6 years before.

Our approach thus allows for a much sharper and more informative analysis of the ensemble of RCT data on a particular way of screening for a particular cancer .. and it will handle different screening schedules, not just across trials, but , as in the ERSPC, WITHIN a single trial (as you know, some of the commentators were a bit disparaging about this aspect of the ESPC.. we think our approach can take proper account of these. Instead of dividing up the ERPSC data but the frequency of screening used, our model will take advantage of all of the data as one.

The other benefit of our approach is that some trials were stopped when a statistically significant difference emerged and the participants in the no-screening arm were then invited to screening. This has complicated the data-analysis. Our method can handle that, just as it can handle the interruptions in funding (and screening) that occurred in Mandel's trial in screening for colon cancer.

So, I hope this has given you a rough idea of what we are proposing, and what we would be asking of the investigators of the various trials.

We are submitting a funding proposal for the March 1 deadline of the Canadian Institutes of Health Research (CIHR). We will be asking for funds to help each RCT PI to 'dig out' the numerators in question. We realize that some of the trials (especially in breast cancer) are already 'long-since' put way, but we hope that even if the computer files are no longer even computer-readable (some are probably on computer tapes in some dusty vaults) but we strongly suspect that there are paper listings of the deaths.. or that just the location in 2-D time of each death can be reconstructed.. For example, in the Malmo breast cancer trial, the numbers involved are in the single digits, and that is even before we divide them along the second time dimension! What is striking in fact is how SMALL some of the numbers

of deaths are in the individual trials.

Of course, once we get down to the details, it will be very interesting to see how resourceful people can be about the reconstruction. We think that once they see the prospect of correctly estimating the parameters from the entirety of the trails, it will be quite motivating and worthwhile. Everyone, from the subjects who participated, to today's generation pondering whether they should be screened, and the funders pondering whether they should pay, deserve better than the time-blind 'meta-analyses' that seem to be increasingly guiding public opinion and public health policies regarding screening.

And we think that when we remove the dilution caused by averaging, the reduction estimates will be boosted, in some cases (e.g, ERSPC) quite a bit.

****

Here is our request for co-operation in the short term.

******* critical (time-sensitive) portion of email *****

By February 20, would you be able to email us indicating how receptive you are to the general idea, and whether you would be willing to encourage other investigators in your field (and investigators who have performed screening trials in other cancers, but in your country..) to come on board.

We are not asking that you invest $$ resources in this. We are planning to ask our CIHR for the funds for you or us to do the data-recovery.

We expect that the question of feasibility and co-operation will be raided by the grant review committee.

We are also open to suggestions as to how PI's are recognized in this area. A PhD student in our biostatistics program here will need to be the first author on a few of the papers from this project -- particularly the ones dealing with the statistical methods -- but we are open to all other options..

Obviously, the more specific you can be as to how confident you are that you can share the data-counts, or that we can reconstruct them from what you have, the better. It is important to mote that the statistical methods do not require individual data, and so we do not see any 'data-privacy' issues or issues of data crossing borders.
we are merely interested in numerators, split up along 2 time-dimensions.

Yours sincerely

James Hanley

[http://www.biostat.mcgill.ca/hanley]

(for our research team:

****** our research team: *********

Prof. Nandini Dendukuri

[biostatistician, works in heath technology assessment, and is an expert in Bayesian methods, which we may need for fitting the models]

Prof. Erin Strumpf

[Health economist, works on cancer screening]

PhD student Zhihui (Amy) Liu

[biostatistics student under our direction;
will refine, implement and test the fitting of the
statistical model described above.]

Myself

[biostatistician; long interest in cancer, starting with
my involvement in cancer clinical trials (with M Zelen)
in Eastern Co-operative Oncology Group [ECOG] and
Radiation Therapy Oncology Group [RTOG] in the 1970s;
sabbatical year at Cancer unit of WHO in 1985-86;
co-author, with M McGregor and others, of report to
Quebec Ministry of Health in mid 1990s on whether
ministry should pay for PSA tests;
author of 3 papers on the appropriate way to analyze data
from cancer screening trials:

1. 2005 Epidemiology. showed benefits of time-specificity,
and how it can recover 'signals' and 'hiatuses' hidden
in cumulative mortality rates. Figure 1 in that article
illustrates the 'convolution' technique we plan to exploit
in the proposed work.

2. 2010 J Medical Screening article: re-analysis of ERSPC: showing more clearly, and quantifying, the timing and extend of the reductions in
prostate cancer mortality produced by PSA screening.

3. 2011 Epidemiologic Reviews article documenting the inadequacies of the
prevailing data-analysis techniques applied to cancer screening data. The findings in that review are what prompted the current application for funding.

1. Links to online information on provincial screening programs

British Columbia Cancer Agency. Screening Mammography Program (SMP) of BC [http://www.bccancer.bc.ca/PPI/Screening/Breast/default.htm]. cited 2009 Jul 1

Alberta Cancer Board. The Screening Program [http://www.albertahealthservices.ca/services.asp?pid=service&rid=1024851]. cited 2009 Jul 1

Saskatchewan Cancer Agency. Screening [http://www.saskcancer.ca/Default.aspx?DN=3f3b564f-a7d1-4bee-bb80-0ec8f2b6b5d4]. cited 2009 Jul 1

Cancer Care Manitoba. Manitoba Breast Screening Program [http://www.cancercare.mb.ca/home/prevention_and_screening/general_public_screening_programs/manitoba_breast_screening_program/]. cited 2009 Jul 1

Cancer Care Ontario. Breast Screening [http://www.cancercare.on.ca/pcs/screening/breastscreening/]. cited 2009 Jul 1

Gouvernement du Quebec, Santé et Services Sociaux Quebec. The Quebec Breast Cancer Screening Program (PQDCS : Programme québécois de dépistage du cancer du sein) [http://www.santepubmtl.qc.ca/mdprevention/fiches/sein/program.html]. cited 2009 Jul 1

New Brunswick Department of Health, New Brunswick Cancer Network. Cancer Prevention and Screening [http://www.gnb.ca/0051/cancer/prevention_screening-e.asp]. cited 2009 Jul 1

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Canadian Breast Cancer Network. PEI Breast Screening Program [http://www.cbcn.ca/en/?section=2&category=1560&regionid=&page=6928]. cited 2009 Jul 1

Alberta Health Services, Alberta Cancer Board. Alberta Colorectal Screening Program [http://www.cancerboard.ab.ca/PS/Screening/Colorectal/]. cited 2009 Jul 1

CancerCare Manitoba. Manitoba Colorectal Cancer Screening Program [http://www.cancercare.mb.ca/home/prevention_and_screening/

general_public_screening_programs/
manitoba_colorectal_screening_program/]. cited 2009 Jul 1

Cancer Care Ontario. Colorectal Cancer Screening [http://
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Analysis of Mortality Data From Cancer Screening Studies

Looking in the Right Window

James A. Hanley

Background: Appropriate statistical analysis is required to measure the impact of early detection and treatment of cancer. The current practice of using cumulative mortality ignores both (1) the delay between early treatment and the time that any averted deaths would have otherwise occurred, and (2) cessation of these delayed benefits some time after screening is discontinued.

Methods: We use time-specific mortality density ratios to estimate the mortality ratio in the "window of influence." We then use time-specific incidence density ratios to assess the extent to which the removal of polyps and other possibly precancerous lesions detected by fecal occult blood screening reduces the incidence of colorectal cancer.

Results: Applied to a theoretical example, the current practice of using cumulative mortality substantially underestimates the reduction in mortality achievable by early treatment. If there is sufficient time for the full impact to emerge, time-specific mortality patterns provide a more accurate measure. In a previous analysis of the screening study, the reduction in cumulative incidence in the screened groups was just under 20%. In our reanalysis, yearly incidence density ratios indicate that had screening not been interrupted, there might have been a 40% reduction in incidence.

Conclusions: Time-specific mortality ratios provide a more sensitive measure of the effects of early detection and treatment. Measures based on cumulative mortality are diluted by inclusion of deaths that occur soon after the initiation of screening as well as deaths that occur too long after the cessation of screening.

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In the design of trials to assess the mortality reduction resulting from screening-induced early interventions against cancer, considerable care is taken to generate high-quality data. The statistical analyses of these data usually measure the reduction in cumulative mortality. Unfortunately, by mixing "irrelevant experience with the relevant experience,"[1] these analyses underestimate the impact of early intervention. We discuss a data analysis principle, long established but seldom practiced until recently,[1–3] and illustrate its sharpness by an unusual example.

The purpose of cancer screening is to detect and treat a lesion now that if left to present itself at a later date would prove fatal x years from now. If such early treatment is successful, the resulting "cure" will contribute to a deficit of mortality x years from now, ie, there will be fewer cancer deaths at that time. Deaths that are averted by today's early treatment, but that would not have been averted by later treatment, create a delayed shortfall that will be distributed within some future time window. Outside this window, cancer mortality statistics will resemble those in a nonscreened population.

Figure 1 shows the reductions in cancer deaths in a hypothetical situation in which screening is carried out for 10 years. For example, as a result of the screening activities in year 1, the earlier detection and associated earlier treatment averted 1 death that would otherwise have occurred in year 5, 2 that would have occurred in year 6, and so on (13 in all). As a result of the *several* years of screening, the total numbers of deaths that would otherwise have occurred in years 5, 6, 7, . . . are 1, 3, 6, ... The totals remain in steady state (13 averted deaths) in years 10 to 14. Because of the cessation of screening in year 10, the "deficits" diminish from years 15 onward; the last deficit is visible in year 19. In the absence of 10 years of screening, there would be no averted deaths. The curve in the bottom of the figure contrasts the mortality in the presence and absence of screening (assuming equal amounts of experience): the mortality rate ratio is 25/25 = 1.0 for years 1 to 4; it falls to 24/25 = 0.96 in year 5, to 22/25=0.88 in year 6, and so on. Using *cumulative* mortality up to years 10, 20, and 30 (30

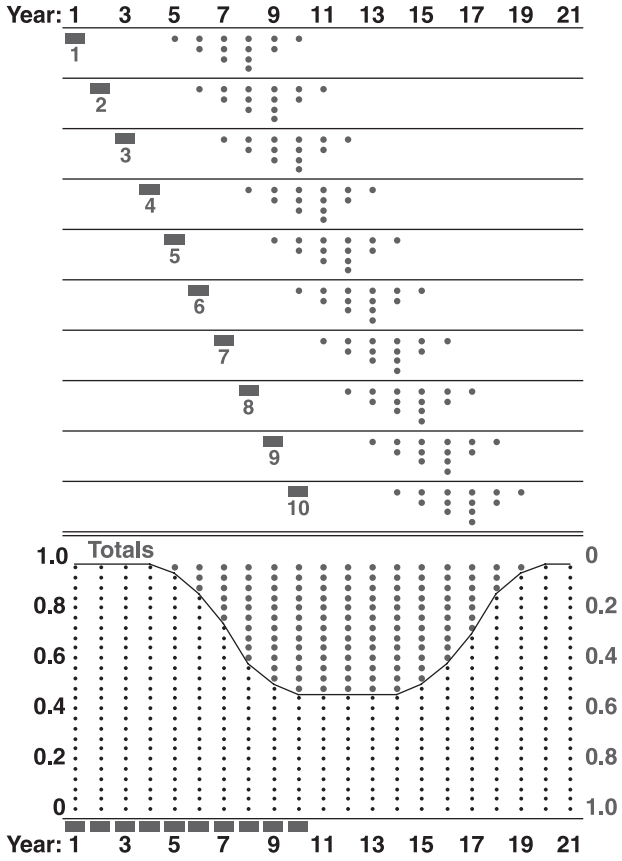

FIGURE 1. Reductions in cancer deaths in a hypothetical situation in which screening is carried out for 10 years. The dots in a specific row in the upper part of the figure represent the deaths averted by that year's screening; the dots in the region entitled "totals" in the lower portion of the figure represent the aggregated numbers of deaths averted, whereas the smaller dots represent deaths that are not averted. The curve represents the mortality rate ratio (left vertical axis) and its complement (right vertical axis).

not shown), the apparent reductions associated with screening are 1–205/250 = 18%, 1–370/500 = 0.26%, and 1–620/750 = 17%, respectively. In contrast, the reductions are 35% and 52% if averaged over years 5 through 19 (any manifestation of effect of early treatment) and 10 through 14 (maximal manifestation), respectively.

Relative to the yearly numbers of deaths in the absence of screening and early treatment, each separate cycle produces its own "deficit" or "trough." The left "lip" of each trough reflects the delay between the time when cancers are detected at a curable stage and when they would otherwise have been fatal. Deaths that occur earlier were not averted by the screening diagnosis and treatment, because the cancer was already incurable at the time of screening. The right lip (where again no deaths are averted) reflects the limits of the "reach" of the screening instrument—a feature that is discussed subsequently. The width of each separate trough reflects the person-to-person variation in "x", whereas the volume of the trough reflects the overall impact of the single application. Continued regular cycles of an effective screening program eventually produce a steady state. If screening is discontinued, cancer mortality among the screened persons reverts to what one would observe with no screening as the last of the delayed deficits are expressed. The parametric relations in Figure 1 are described in more detail in Miettinen's analysis.[1]

The principle of looking in the appropriate window after initiation of screening is widely appreciated by those who examine nonexperimental data on screening. For example, investigators[4–8] and commentators[9] have assessed whether the extensive prostate-specific antigen (PSA)-based screening begun around 1990 has produced corresponding shortfalls in prostate cancer deaths in the early 2000s. Appropriately, none of these assessments considered the declining prostate cancer death rates in some countries in the early 1990s as evidence of the benefits of PSA-based early detection and treatment, nor did they take unchanged rates in other countries as evidence that earlier treatment had no impact. After all, PSA-based screening was not even available in the 1980s to detect—at a curable stage—the cancers that proved fatal in the early 1990s. The pattern of prostate cancer mortality soon after the introduction of PSA was uninformative and correctly ignored. Similarly, to study the impact of the NHS Breast Screening Programme, which was initiated in Wales in 1991, Fielder and colleagues[10] focused on deaths from breast cancer among women who were diagnosed after the program began and who died *after 1998*.

Curiously, it is in studies in which experimental data have been available—from randomized clinical trials of screening for cancer of the breast, colon, and lung—that the principle of "looking in the right window" has been more neglected. Morrison's textbook[11] devotes a few sentences to this principle; but it then goes on, in all of the examples, to compare cumulative mortality—over the *entire* period of screening and follow up—in the screened and unscreened groups, no matter how long the duration of screening. Until recently, other investigators have done the same.

Caro and McGregor[2] were apparently the first to use this data analysis principle. In a report to the Quebec health ministry, they state: "The difference in cumulative mortality obscures the effect of screening because there is a lag of several years between screening and the time that deaths would have otherwise occurred and, thus, mortality during these early years cannot be influenced by screening. To obtain more revealing estimates requires translating the reported figures to time-specific breast cancer mortality rates (incidence densities)."

The first to reiterate the principle explicitly in the open literature appears to have been Miettinen.[1,3] Much of the quote in the previous paragraph is a paraphrase of his arguments. When he applied this principle to the data from the Malmö mammographic screening trial, in which other authors could see little impact on mortality,[12] the impact became much clearer and stronger.

His reanalysis prompted me to revisit the data from another cancer screening study that we had previously used (without questioning the data analysis) in our graduate teaching in epidemiology.

EXAMPLE AND METHOD

In 1999, Mandel et al[13] reported the latest results of a large U.S. randomized trial of the effect of fecal occult blood screening on colorectal cancer mortality. In 2000,[14] they reported the effect on the incidence of colorectal cancer. A total of 46,551 people were recruited between 1975 and 1978 and randomly assigned to annual screening, biennial screening, or usual care. The incidence end point makes this a particularly sensitive model because of the shorter time scale between action and impact: the focus of the analysis was the impact of discovering and removing polyps and other precancerous lesions that might otherwise (in the absence of this screening and removal) become cancer. A second, unplanned feature of this trial was the pattern and duration of screening. Screening was conducted between 1976 and 1982 and, after a hiatus resulting from a lack of funding, resumed in 1986. All screening was completed in 1992.

The reanalysis presented here is based on the patterns of incidence of colorectal cancer in the first 18 years of the study. In the original report, the authors calculated the ratio of the 18-year cumulative incidence of colorectal cancer in each of the 2 screening groups to the incidence in the control group.[14] This ratio was used to measure the extent to which screening affected incidence. Relative to the control group, the 18-year cumulative incidence ratios were 0.80 and 0.83 for the annual screening and biennial screening groups, respectively.

Our analysis is based on the numbers of cases of colorectal cancer reported in Table 1 of the article (417, 435, and 507 respectively); the numbers at risk at years 0, 2, . . . ; 18 reported at the foot of Figure 1, and the plotted cumulative incidence for each year.[14] From these pieces of information, the numbers of new cases of colorectal cancer for each separate year after the introduction of the program were reconstructed. Because the patterns in the 2 screening arms did not differ much, they were combined. The yearly incidence ratios for the screening group relative to the control group were then calculated using the moving averages of the data for 3 adjacent years.[1,3] Because the focus here is on avoiding bias in point estimation, interval estimates[1] are not shown.

RESULTS

Part A of Figure 2 shows the cumulative incidence of colorectal cancer in the screened and unscreened study groups for each of the 18 years of follow up. The reported reduction in incidence in the screened groups (just under 20%) reported by Mandel and colleagues was based on the cumulative incidence at 18 years. Our yearly incidence density ratios, shown in part B, yield a stronger and more visible "signal." This new analysis highlights the lag from screening to impact, the lag from the discontinuation of screening to the loss of impact, and (after the resumption of screening) the lag from screening to impact. It suggests that had screening continued uninterrupted, there would have been a sustained reduction in incidence of at least 40%. This interpretation is different from that in a review,[15] which stated, "In the U.S. study, colorectal cancer incidence rates were reduced by 20% and 17% in the annually and biennially screened groups, but only after 18 years. No incidence reduction has been observed in either of the 2 European studies, both of which have offered the test at 2-yearly intervals, although the cohorts have been followed for only 13 years so far, and at that stage no effect on incidence was discernible in the US data."

DISCUSSION

In many studies focusing on cancer mortality, the reductions may be obscured or minimized by a number of

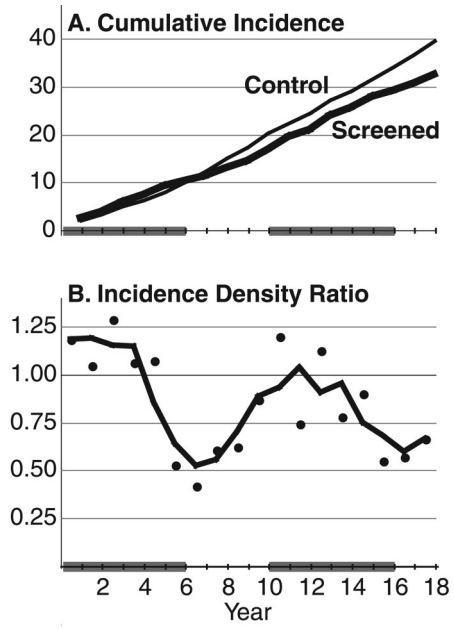

FIGURE 2. Colorectal cancer in the unscreened and screened study groups (annual and biennial combined) based on data in Mandel et al.[14] The 2 6-year periods when screening was conducted are shown as thicker lines on the time axis. Cumulative incidence (**A**) is per 1000. Yearly incidence density ratios (**B**) are shown as points.

factors: person-to-person variability in the delay until the averted deaths would have occurred, few screening cycles, limited uptake and adherence, and random variation because of small numbers of deaths. The study reanalyzed here focused on cancer incidence, and on the impact of detecting and removing polyps and other precancerous lesions that might otherwise become cancer. Although the several screening cycles and good compliance helped to create a large impact, the magnitude of this effect is underestimated if one measures it by reductions in cumulative incidence. In contrast, the yearly incidence density ratios provide an undiluted measure of the impact. In addition, the ratios allow the delay to be estimated directly from the data.

This particular cancer incidence example was chosen because the data were reported in sufficient detail for reanalysis. In addition, the unusual pattern of screening and follow up generated a complex "output function" that was much more readily discernible using uncumulated data. However, the principle is a general one; it applies with greater force (using its counterpart, yearly mortality density ratios) to studies that seek to quantify the reduction in mortality achieved by early detection and treatment of already malignant lesions. Indeed, mortality ratios leave less room for misinterpretation than incidence ratios: the reduction in colorectal cancer incidence might simply reflect an advance in the diagnosis of prevalent already malignant lesions rather than a true reduction in future incidence caused by the removal of precancerous lesions. The fact that the incidence density ratio does not exceed 1.0 when screening was reinstituted suggests that this alternative explanation does not account for all of the observed pattern of incidence density ratios.

It should be noted that the time-specific mortality density ratios do not require prior specification of the "window of influence." Rather, if there is sufficient screening and follow up, its location is revealed by the data themselves.

The fact that the pattern of observed mortality ratios is a function of the duration of screening and follow up has an important implication for metaanalysis of data from screening studies. Because each study screens for a different duration, with a different screening interval, and follows up subjects for a different length of time, the locus and shape of its mortality–density–ratio curve will reflect its unique time pattern of screening. If there is one comparative parameter that makes sense for metaanalysis, it is the maximal depth of the trough theoretically achievable with continued screening. However, one must first consider whether the screening and follow up lasted long enough to expose the maximal impact. This prerequisite is discussed in more detail in Miettinen's commentary on the pooling of results from 2 mammographic screening studies with very different screening and follow-up patterns.

In most instances, the impact of screening is obscured if the screening duration or follow up is too short. At the other extreme, too much follow-up time after the discontinuation of screening, with cumulation of all deaths regardless of their temporal pattern, can also obscure the impact. For example, the report on the extended (24-year) follow up of the Mayo Lung Project examined "whether additional time would allow for a reduction in lung cancer mortality to be observed in this arm."[16] Lung cancer mortality in the intervention arm (intensive screening) over the entire block of 24 years was compared with the corresponding average rate in the usual care arm. The rate in each arm was based on *all l*ung cancer deaths from those in the very first year (deaths that could scarcely have been influenced by detection and slightly earlier treatment) through the end of intensive screening at 6 years up until the end of follow up 18 years after intensive screening was discontinued. Tumors that proved fatal in the later years of follow up must have been well beyond the temporal "reach" of screening during the first 6 years. This strategy of including deaths for several years beyond the impact of the last screening is the temporal analog of evaluating the benefits of screening sigmoidoscopy but including deaths from cancers located beyond the reach of the sigmoidoscope. Including these deaths outside of the "window of influence" associated with the screening dilutes whatever impact (beneficial or otherwise) the early detection and treatment might have already had on lung cancer mortality. If intensive screening and the resultant earlier treatment were indeed effective, time-specific mortality ratios would be more likely to show it; they would also show the length of the lag until the impact becomes apparent and the eventual loss of impact after discontinuing screening.

The emphasis here is the effectiveness of screening in organized trials, but the same principle of the appropriate time window applies to case–control studies,[17] which have the added challenge of minimizing any effects of subject self-selection. However, possibly because the approach is nonexperimental, and also possibly because of the "after-the-fact" perspective that is inherent in case–control studies, these investigators using the case–control approach seem to appreciate the importance of the appropriate window more fully than their clinical trials counterparts.

Although it can be difficult to decide what constitutes "recent" and "distant," the principle of ignoring irrelevant distant and recent exposure to a putative etiologic agent, based on the concept of "latency," is commonly applied to data analyses in (etiologic) research into the unintended effects of an agent. The analysis of data from trials of cancer screening needs to reflect the fact that when cancers are cured by today's early detection and treatment, but would not have been if detected and treated later, these cures only becomes apparent after some delay. Fortunately, if they are allowed to, the data will ultimately speak for themselves.

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IN THE NEXT ISSUE

Coming in January (Selected papers)

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Analgesic drug use and risk of ovarian cancer

***EPHX1* polymorphisms and the risk of lung cancer: A HuGE review**

Breastfeeding and overweight in adolescence

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Xenobiotic-metabolizing genes and small-for-gestational-age births: Interaction with maternal smoking

Smokeless tobacco use and risk of stillbirth

ORIGINAL ARTICLE

Mortality reductions produced by sustained prostate cancer screening have been underestimated

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See end of article for author's affiliations

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Background The recently published European Randomized Study of Screening for Prostate Cancer (ERSPC) reported prostate specific antigen (PSA)-based screening to have reduced the prostate cancer death rate by only 20%. However, this is an underestimate caused by (i) including in the 20% the years before the impact of the first screen becomes manifest, and (ii) not having full information for the follow-up years where the effects of the screening are most apparent. This paper provides a re-analysis of the results using time-specific measures, which avoid the first of these sources of error.

Methods Mortality rate ratios for follow-up years 1–12 were derived from the yearly numbers of prostate cancer deaths and numbers of men being followed in each arm of the ERSPC. To reduce statistical noise, they were based on moving three-year intervals, and a smooth rate ratio curve was fitted to the yearly data, in order to measure the steady state reduction in mortality and to identify the time at which it reached this level.

Results The re-analysis suggests that the sustained reduction in prostate cancer mortality may be more than 50%.

Conclusion Re-analysis of the ERSPC data suggests that if screening is carried out for several years, and if follow-up is pursued until the reduction becomes manifest, the reduction in mortality will be 50–60%. An analysis that includes the 2007–2008 follow-up data is required to quantify more precisely the impact of this intervention.

INTRODUCTION

The European Randomized Study of Screening for Prostate Cancer (ERSPC), which began enrolment 19 years ago, accrued 162,000 men. The ERSPC publication, in March 2009,[1] reported a reduction in prostate cancer mortality due to screening of 20%. This disappointing result has prompted a number of organizations and authorities to rethink their prostate cancer screening efforts and their public health messages.

However, the 20% reduction is a substantial underestimate, for two reasons. First, there is a considerable delay between the time screening starts and the time the effect is expected to be observed; the estimated 20% is an average of the null reductions in years 1–7, before benefits could become apparent, and the substantial reductions that began to appear from year 8 onwards. Second, the (proportional-hazards-type) summary measure (the 20%) is sensitive to the duration of follow-up, which closed at the end of 2006, after an average of just nine years of follow-up (range 3–15). A re-analysis of these ERSPC data that uses yearly rate ratios to avoid these two sources of error suggests a mortality reduction, due to screening, of more than 50%. However, a more precise measure will not be available until the critical data from 2007 and 2008 (and beyond) are included in the analysis.

METHODS

Five randomized trials of prostate cancer screening have now been reported. The numbers of men invited to the screening arm in the two Swedish studies[2,3] were 1500 and 2400, respectively. The Quebec[4] and USA[5] studies enrolled a combined total of 123,000 men (69,000 in the combined screening arms), but in each of these two studies the actual screening activities in the screening and control arms differed so little that at best only a small difference in prostate cancer mortality could be expected. The ERSPC enrolled 162,000 men aged 55–69 years at intake. The larger sample size and substantial difference in the participation rates in the two arms meant that it has considerably greater resolving power.

In the ERSPC report, the effect of screening on prostate cancer mortality was expressed as one number, derived from the numbers of prostate cancer deaths over the *entire* period of observation available for each man (range 3–15, average 9 years). Over this period, there were 214 prostate cancer deaths in 643,401 man-years of observation in the screening group and 326 in 785,585 man-years in the control group. These are the basis for the reported rate ratio of 0.80, and the conclusion that 'prostate specific antigen (PSA)-based screening reduced the rate of death from prostate cancer by 20%' (95% CI: 2–35%). The article in the *New England*

Journal of Medicine[1] (*NEJM*) also contained a graph showing, for each arm, the 'cumulative risk' of death from prostate cancer. The two curves in this key graph are redrawn in the current Figure 1a. On the basis of these curves, the authors did note that 'the rates of (prostate cancer) death in the two study groups began to diverge after seven to eight years and continued to diverge further over time'. This divergence is here quantified, because it provides a more appropriate and meaningful measure of the reduction in mortality produced by screening than the reported 20% figure.

When studying the results of interventions which have virtually immediate effects, such as vaccinations,[6] many medications[7] and screening for abdominal aortic aneurysms,[8] it is logical to cumulate the outcome events from the time the intervention commenced, and to report a single rate ratio derived from a proportional hazards model. However, as is seen in Figure 1a, there is a delay of several years until the benefit of prostate cancer screening becomes manifest and a single average mortality reduction, obtained by cumulating all prostate cancer deaths, will

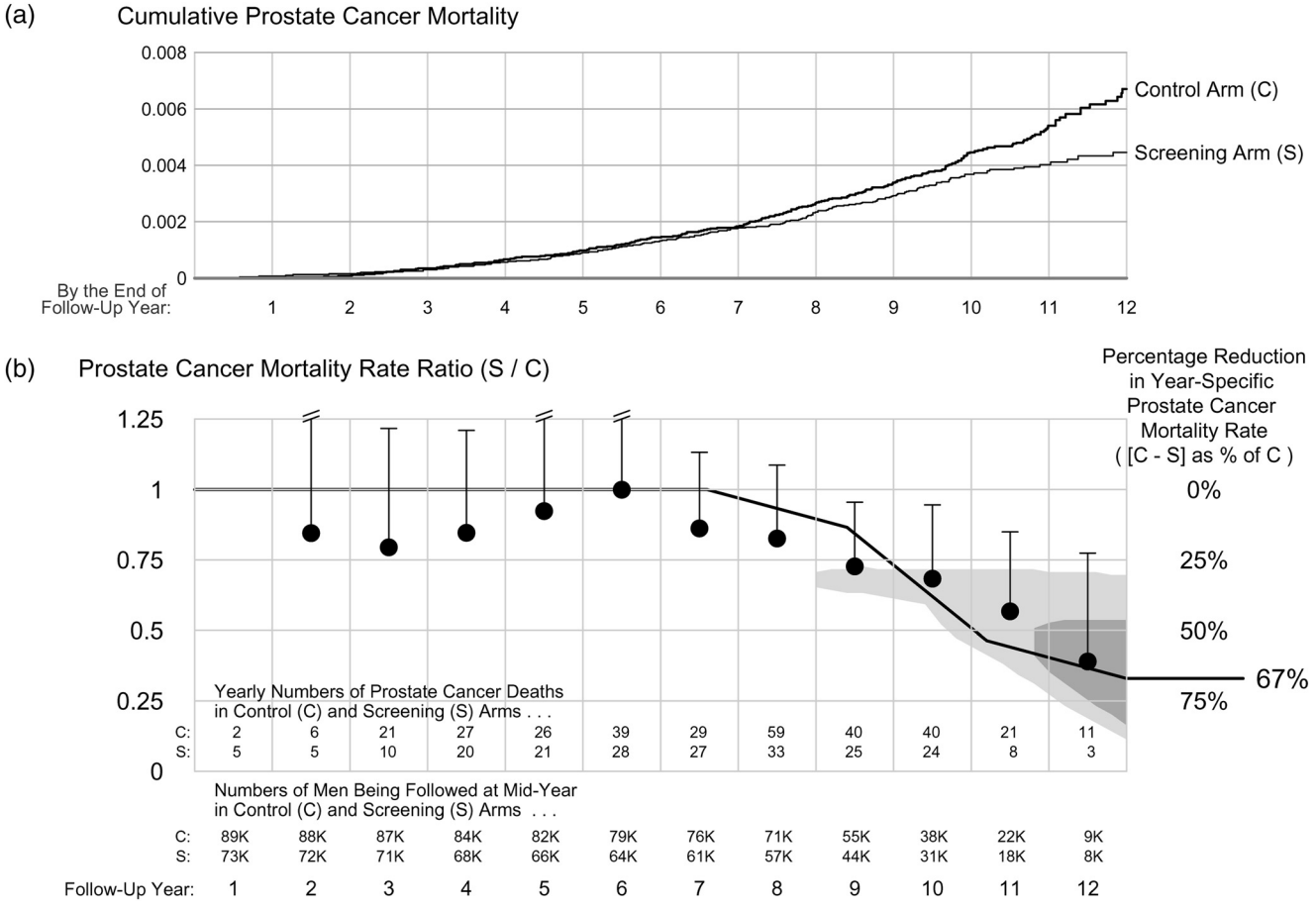

Figure 1 Comparison of prostate cancer mortality rates in two arms of European Randomized Study of Screening for Prostate Cancer (ERSPC). The graphs and numbers in this figure are based on the individual-patient-data extracted from the individual-level postscript commands used in Figure 2 of the *NEJM* report. For details on how these individual data were extracted, see the Methods section of the present report. (a) Cumulative mortality curves, presented in the same format as in the original publication. As noted by the authors, 'the rates of (prostate cancer) death in the two study groups began to diverge after seven to eight years and continued to diverge further over time'. However, they included the years of zero effect in their estimate of a reduction of overall average mortality of 20% (mortality rate ratio 0.80). 'This is not an appropriate measure of the impact of screening, since the numbers of cures attributable to the screening in year 1 to year *T* only become apparent (as lower mortality rates in the screened than the control arm) in year (1 + ?) to year (*T* + ??)'. Note that *T* varied somewhat across the seven ERSPC countries, and is used in a generic sense here. (b) Yearly prostate cancer mortality rate ratios, used for re-analysis. These are designed to measure the timing and extent of the prostate cancer mortality reduction in years (1 + ?) to (*T* + ??) as a result of the screening in years 1 to *T*. Each rate ratio was calculated by dividing the observed rate of prostate cancer deaths in the screening arm by the corresponding rate in the control arm. The rate ratio shown above a given year is based on the data for that year together with the data in the years immediately preceding and following it. The upper end of each vertical line denotes the upper 95% limit of the percentage reduction in prostate-cancer mortality: the reductions in the three-year intervals centered on years 9 and beyond are statistically significant. The dotted line, with an asymptote of 67%, beginning at 12 *years*, was fitted using the method of maximum likelihood (see Appendix A). The two shaded regions represent the 50% and 80% confidence regions for these two parameters. The 80% CI associated with the 67% asymptote, derived from the vertical range of the lighter grey region at 12 years, is 30–89%. The results of the re-analysis using time-specific rate ratios indicate that the cures attributable to the screening in study year *t* only begin to become statistically apparent by year *t* + 7 and later. They also indicate that of those in the control arm who died (or will die) of prostate cancer in years 8–12 of the study, possibly as many as half of them would not have died of prostate cancer had they been offered the programme. The 25–60% reductions seen in years 8–12 of the study suggest a much greater numbers of cures attributable to the screening in year 1 to year *T* than the single overall 20% figure reported in the original article, but further follow-up data are required to make a precise estimate

underestimate the effect.[9–11] This underestimation is considerable if the period of follow-up before the intervention has any effect makes up a substantial portion of the entire period of follow-up available. Underestimation will also result if the follow-up does not extend far enough to include the period when the effects of sustained screening become most apparent. Both the timing and extent of the reduction become much more evident if one examines prostate cancer mortality in intervals of the follow-up (one-year intervals will be used here).

Therefore, *year-by-year* mortality rate ratios were derived from the yearly numbers of prostate cancer deaths and numbers of men being followed in each arm. To do so, the pdf file containing Figure 2 of the *NEJM* report was saved into an encapsulated postscript (eps) file format, and from this eps file, the exact information was extracted (namely, the coordinates of the line segments and dots) that the statistical programme, Stata, had used to draw the two Nelson–Aalen cumulative hazard curves. The eps file contained the exact coordinates of each of 89,308 and 72,837 line segments or dots, *one per man*. The horizontal and vertical coordinates of each of these segments/dots provided the exact numbers of men being followed at each point in follow-up time, and thus at the exact times of the vertical steps in the curves (corresponding to prostate cancer deaths). The number of prostate cancer deaths at each time point was obtained by multiplying the size of the step by the number being followed at that time. The numbers were then aggregated by year and study arm to produce the counts listed in Figure 1b.

Given the paucity of follow-up beyond year 12, the re-analysis was limited to the yearly mortality ratios for each of the first 12 years. To reduce the statistical noise, these were based on the deaths in moving three-year intervals, so that the ratio and upper limit of the 95% CI shown above a given year are based on the data for that year together with those in the years immediately preceding and following it; those for year 12 are based on the numbers of deaths in years 11 and 12 combined. The total number of prostate cancer deaths in year one was fewer than 10, and so a rate ratio for this first year is not shown.

Despite this strategy to reduce noise, the observed prostate cancer mortality rate ratios in the ERSPC study did not follow a perfectly smooth time-curve. This is understandable, as each of the two numerators that contribute to each observed rate ratio is subject to separate Poisson variation that is substantial when event rates are low; the observed fluctuations may also reflect the merging of data from seven ERSPC countries with somewhat differing screening intensities and differing durations of follow-up. Thus, in order to measure the steady state reduction in mortality, and to identify when it reached this level, as precisely as the data allow, a formal statistical procedure was used to fit a smooth rate ratio function to the mortality data, grouped into bins 1/5 of a year wide. Candidate curves used were those with the same general form as the one fitted in Figure 1b, because repeated four-year screening interval was used in the countries that contributed more than 80% of the men, and the death rate in the screening arm would not be expected to have begun to revert upwards towards that in the control arm until after the end of year 12. The curve has three parameters, when the mortality rate ratio first declines, the steady state *reduction* that is reached, and *when* it is reached. The *when* (i.e. the length of the delay until the reduction reaches a steady state) is a function of the screening regimen, and cannot be specified in advance, although it is expected to be several years. Thus it was derived from the observed data, using the method described in the Supplementary Material. The use of a formal curve-fitting approach to provide the best-fitting values of the curve's three parameters removes the element of subjectivity: otherwise, different readers might 'see' different degrees of reduction in the same set of rate ratios shown in Figure 1b.

RESULTS

The yearly numbers of prostate cancer deaths in each ERSPC arm, along with the mortality rate ratios for the intervals centered on years 2 to 12, are shown in Figure 1b. They indicate that after an expected delay (which the data indicate is approximately 7 years), the prostate mortality reductions that become evident in years 9 and beyond are statistically significant and considerably greater than the reported 20% reduction in the rate of prostate cancer deaths.

A formal curve fitting was also performed. Not surprisingly, the best (Maximum Likelihood) estimate is that, although the rate ratio became non-null starting at approximately 6.5 years, the steady state reduction has not yet been reached: the point estimate so far is a sustained 67% reduction (80% CI: 30–89%) beginning at year 12. Moreover, as can be seen from the wide confidence region, the numbers of deaths are not sufficient to establish its timing and magnitude more precisely.

DISCUSSION

The 'downsides' of PSA-based prostate cancer screening are well documented and accepted. In order to document the 'upside', five randomized trials (the first of which began 23 years ago), involving 321,000 men in 10 countries and with an average follow-up ranging from 7 to 15 years, have sought to measure the reductions in prostate cancer mortality achievable by this screening. The first Swedish study used a 1:5 randomization to enrol 1500 men in the screening arm; the first two rounds of screening, in 1987 and 1990, involved digital rectal examination (DRE) only, while those in 1993 and 1996 added PSA. While 78% of the screening invitees underwent some screening, half of the men with screen-detected tumours did not receive any treatment after diagnosis. Some 1.3% of those invited, and 1.3% of those not invited, had died of prostate cancer by March 2003. In light of these features of the trial, the mortality ratio of 1.0 and the associated 95% CI of 0.6–1.6 are not surprising. In the other Swedish study, which used a 1:10 randomization, 2400 men were invited to one round of screening involving DRE and PSA. Some 74% invitees accepted; only 11 of the 41 men offered treatment with curative intent for their screen-detected cancers underwent radical prostatectomy, while 'the remainder were offered treatments which today are considered obsolete'.[3] Thus, the prostate cancer mortality ratio of 1.1 and associated

95% CI of 0.8–1.5 were, again, to be expected. The screening in the Quebec and US studies, begun in 1988 and 1993, respectively, involved PSA from the outset, and involved more sizeable numbers of men (47,000 randomized 2:1, and 77,000 randomized 1:1, respectively), and repeated PSA-based screening. However, there were only limited differences in the actual screening activity in the contrasted arms in each trial. Only 24% of the invitees in the Quebec trial were screened. Whereas the rates of compliance in the screening group in the US trial were 85% for PSA testing and 86% for DRE, the rates of screening in the control group were also very high, increasing from 40% in the first year to 52% in the sixth year for PSA testing and ranging from 41% to 46% for DRE. Moreover, the results of the US study are largely driven by prostate cancer deaths in years 1–7. In light of these features and in light of the timing of the reductions one would expect in a trial with a larger contrast in screening activity *and* sufficient follow-up, the absence of a mortality reduction in the Quebec and US trials is also not surprising. The much larger ERSPC, with its much larger difference in screening activity in the two arms, had considerably greater resolving power. Even though this resolving power has not yet been fully utilized to measure the signal in the very follow-up time-window where it is probably strongest, this potential can be achieved merely by collecting additional data.

It should not be concluded from the ERSPC report that the best expectation of PSA screening is a reduction in prostate cancer mortality of 20%. The time-specific re-analysis of the prostate cancer deaths in the first 12 years of follow-up suggests that if screening is carried out for several years, and if the follow-up is pursued into the window where the reduction in mortality becomes manifest, the reduction to be seen there will be 50–60%. However, although the ERSPC report was published in March 2009, the follow-up ended in December 2006, just when the pattern had begun to emerge. Thus, with the limited observations in the window where the screening benefits are expressed, it is not possible to put precise statistical bounds on this reduction, and so the prostate cancer deaths from 2007 onwards are crucial to more precisely measure the reduction achieved.

The re-analysis using yearly rate ratios avoided the dilution caused by averaging seven years of (expected) non-reductions with five years of increasingly greater reductions, but it was not able to avoid the dilution and imprecision caused by inadequate follow-up. An analysis that includes this missing follow-up and that employs a time-specific approach is awaited.

Whatever full mortality reductions emerge, those who might wish to 'purchase' them need to know how much they cost. Some may well consider that even if screening could achieve a sustained reduction of 67% (or even 97%), the very low prostate mortality rates in the control group means that the small absolute reductions will be achieved at an unacceptable cost.[12] (So far, only 326 or 0.36% of the 89,353 men in the control group have died of prostate cancer; our theoretical calculations suggest the number will approximately triple by follow-up year 20.) However, all would agree that biases in the estimation of benefit need to be avoided. Moreover, in view of the effort and resources that have been expended on the ERSPC thus far, it is worth pursuing a much more precise measure of the mortality reduction than the data in the 2009 report were able to provide.

The present re-analysis follows the intention-to-treat principle, using time-specific rates to reveal the non-proportional hazards pattern expected with screening data. The objective curve-fitting approach used in Figure 1b avoids the need to 'pre-specify' when the reduction reaches steady state; it does specify the smooth form of the rate–ratio curve, but allows the data themselves to inform us about the two essential parameters that determine it, namely the timing and extent of the prostate cancer mortality reduction caused by screening.

A time-specific analysis is, of course, only necessary when the effect of an intervention is delayed, as in the case of prostate cancer screening. By contrast, screening for abdominal aneurysms produces an immediate and sustained reduction in mortality from ruptured aneurysms, and the cumulative mortality, in this case, fully captures the benefit of screening. The results of a programme of screening competitive athletes for potentially lethal cardiovascular abnormalities[13] are a further striking example of the shape of the 'response function' with time, and the role of screening intensity in this. Recognition of the difference between interventions with immediate and delayed effects should prompt similar re-analyses of the data from trials of screening in other cancers, and similar analyses in yet-to-be reported cancer screening trials.

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Supplementary Material for

Mortality reductions produced by sustained prostate cancer screening have been underestimated

1. The need for time-specificity in the analysis of data from cancer screening studies

Figure 1A and Supplementary Figure A show when it is and is not possible to use ratios of overall (or cumulative) cancer mortality rates to measure the timing and magnitude of the reductions produced by screening. Figure 1B includes a smooth-in-time rate ratio curve that was fitted to the ERSPC data. This appendix contains a more extensive discussion of the need for time-specificity, and provides details on how the smooth curve was fitted.

Since the first cancer screening trials, investigators have tried to avoid the dilution caused by including cancer deaths that occur *after* the window in which the benefits of the regimen become manifest[1 2 3]. The recognition that the dilution caused by including those that occur *before* this window is more recent[4 5 6], and the message to avoid it has gone largely unheeded.

This ongoing time-insensitivity in the analysis of screening trials is all the more surprising today, where reviewers routinely ask whether the data justify the use of a proportional hazards model, i.e., of a single (average) hazard ratio. But even if we did not yet have screening data, biological principles alone suggest that this '*constant-over-time right-from-the-outset reduction*' assumption may govern the time-pattern of the effects of screening for some conditions, such as abdominal aortic aneurysms, but *not for cancers*.

What has not been previously recognized is the considerable influence of the duration of follow-up, particularly in prostate cancer where the time scale is longer than for other cancers. Baker[4] termed the dilution caused by including excessive/superfluous years in the time window

after the effect of the *last* screen become manifest "post-screening noise." In contrast, in trials of sustained prostate cancer screening, such as ERSPC, the attenuation is caused by (i) including the years *before* the impact of the *first* screen become manifest, and (ii) *not having full follow-up information available on the years where the effects of the screening are most apparent.*

These distortions argue for a data-analysis approach that cannot be influenced by, and is insensitive to, the choice of the time horizon of interest, the time window in which the effect of the screening regimen becomes manifest, and the amount of follow-up at the time of data-analysis. The measure should be robust to these and be calculable objectively from the data.

In Figure 1B, we subject the ERSPC data to formal quantitative time-specific analysis. Each time-specific rate ratio is independent of the ratio calculated from any another portion of the follow-up. The curve shows the timing of the delay until the effect of the screening regimen is expressed.

2. Fitting a smooth-in-time mortality rate ratio function.

In screening trials, the yearly observed numbers of cancer-specific deaths from the target cancer in each study arm are small, and so yearly mortality rate ratios fluctuate widely. For example, if the *expected* number in the non-screening arm for a particular year is 25, the *actual* count could vary by more than two-fold: under the Poisson law, it could range from about 15 to 35. Similarly, if the expected number in the screening arm was 16 (a true reduction of 36%), the actual count could vary from maybe 8 to 24, so that the observed rate ratio could vary from 0.3 (70% reduction) to 1.2 (20% increase). With event rates of this order of magnitude, it is difficult even with sample sizes in the tens of thousands to objectively estimate the true timing and extent of

the benefit of the intervention "by eye". Thus, a formal curve-fitting procedure becomes important to smooth out the noise.

In this section, we describe – and show how to fit -- the *simplest* candidate curve for the rate ratios characterizing the results of a cancer screening program comprising several rounds of screening. The assumed form of the rate ratio curve (the fitted version is shown as a dotted line in Figure 1B) is such that it has a value of unity for some unknown number of years, begins to descend after this unknown time point, and descends to an 'asymptote' of unknown value some unknown number of years later, and remains at this value thereafter. If this simplest of all models is postulated, there are only three unknowns to be estimated, when the rate ratio began to be non-null, the value of the RR asymptote and the time at which the asymptote began. More complex curves, such as would be needed to smooth curves that show *transient* reductions, can be fitted in the same way, simply by changing the form of *RR(t)* and adding more parameters. To do so, one would, naturally, require more extensive and more detailed data.

Consider a theoretical rate ratio (RR) curve, of the same shape as the one depicted by a dotted line in Figure 1B. Suppose the RR begins to change (become non-null) at T_c, and that its asymptote has the value RR_a, beginning at time $t = T_{begin}$.

Let it be defined as

$$RR(t) = \begin{cases} 1 & \text{until } t = T_c \\ 1-\{0.1, 0.2, 0.5, 0.8, 0.9\}\times(1- RR_a) & \text{from } t = T_c \text{ to } T_{begin} \text{ [5 equal } t \text{ steps]} \\ RR_a & \text{from t =} T_{begin} \text{ onwards} \end{cases}$$

Suppose the data consist of:

the times, $t_1, t_2, \ldots, t_D$, measured from randomization to screening/not, of each of the D prostate cancer deaths in the two arms combined.

the corresponding indicators, $s_1, s_2, \ldots, s_D$, of whether they occurred to men in the screening arm (1) or control arm (0).

the corresponding denominator-ratios, $dr_1, dr_2, \ldots, dr_D$, where dr_i is the ratio of the numbers of men being followed in the screening and comparison arms at the time of the i-th prostate cancer death.

The values of the three parameters, T_c , RR_a and T_{begin} can be estimated by numerically maximizing the Likelihood constructed by treating $s_1, s_2, \ldots, s_D$ as realizations of D Bernoulli random variables, where the expected value of the i-th such random variable is $dr_i \times RR(t_1)/[1+ dr_i \times RR(t_i)]$.[7] The profile log likelihood can be used to obtain a C% confidence region for the RR_a and T_{begin} parameters by searching for those other pairs of these two parameter values that produce 2×ProfileLogLikelihood values that differ by less than a given amount from the value of the 2×ProfileLogLikelihood evaluated at the MLE (this amount is the C^{th} percentile of the Chi-square distribution with 2 df).

The t's, s's and dr's may not be available at the level of the individual, but the numbers of deaths S and NS in the screening and non-screening arms within each say one or half-year interval of follow-up may be known, along with the value of each "denominator ratio" DR, i.e., the ratio of the person-years lived in the interval by those in the screening and comparison arms. With such data, we can use the same conditioning as above, and regard the value of S for interval centered on t_{mid}, conditional on the total number $S + NS$, of prostate cancer deaths in the interval, as the realization of a binomial random variable with expectation $DR \times RR(t_{mid})/[1+ DR \times RR(t_{mid})]$.

The second derivative of the profile Log-Likelihood can be used, along with cancer-specific and all-cause mortality rates, to calculate in advance what precision/power will be achieved with various numbers of subjects and durations of follow-up.

May 3, 2010

Supplementary Figure A

Timing of effects of screening in disease processes with different natural histories: cumulative cause-specific mortality as reported in the Multicentre Aneurysm Screening Study (MASS) and the European Randomized Study of Screening for Prostate Cancer (ERSPC). The MASS enrolled 68,000 men aged 65-74 and involved a one-time screen with immediate treatment or surveillance of detected abdominal aortic aneurysms. As noted by the authors, "The benefit seen in earlier years of follow-up was maintained in the later years of follow-up, with continued divergence of the cumulative curves of deaths related to abdominal aortic aneurysm in the two groups". The overall mortality rate reduction of 48% (mortality rate ratio 0.52) is an adequate and accurate measure of the impact of screening. The ERSPC enrolled 162,000 men aged 55-69 and involved repeated PSA-based screens 4 years apart. As noted by the authors, "The rates of (prostate cancer) death in the two study groups began to diverge after 7 to 8 years and continued to diverge further over time". The overall mortality rate reduction of 20% (mortality rate ratio 0.80) is an inadequate and inaccurate measure of the impact of screening.

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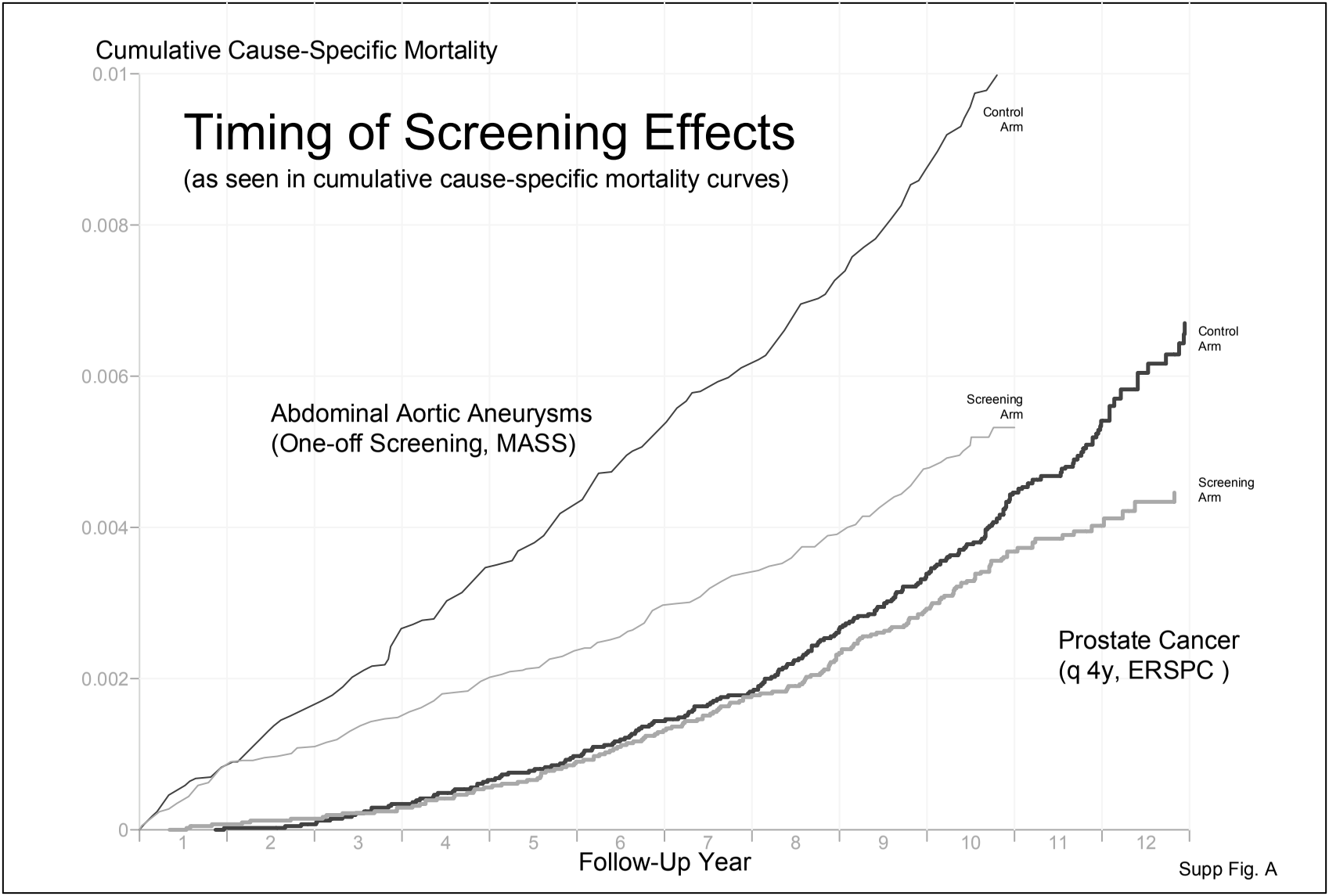
Cumulative Cause-Specific Mortality
Timing of Screening Effects
(as seen in cumulative cause-specific mortality curves)
0.01
0.008
0.006
0.004
0.002
0
Control Arm
Screening Arm
Abdominal Aortic Aneurysms
(One-off Screening, MASS)
Control Arm
Screening Arm
Prostate Cancer
(q 4y, ERSPC)
1
2
3
4
5
6
7
8
9
10
11
12
Follow-Up Year

Supp Fig. A

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Measuring mortality reductions in cancer screening trials

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Abstract

Randomized trials involving large numbers of people and long follow-up have helped measure the mortality reductions achievable by screening for cancer. However, the reported reductions in many of these trials have been modest. Part of the reason for this is the inappropriate way the reductions have been calculated. Analyses have largely ignored the fact that there is a time-window in the first several years after beginning screening in which there cannot be a sizeable mortality reduction, followed by one in which the reductions become evident, and -- unless screening is continued -- a third window in which mortality rates in the screened group revert to those in the unscreened group. This review uses time-specific mortality ratios to address the timing and extent of the reductions achieved in trials of screening for prostate, breast and colorectal cancer; it finds that the mortality reductions reported in the literature substantially have underestimated what might be accomplished with continued screening. The natural history of the disease, the frequency of screening, and the duration of follow-up determine the time patterns in the reductions observed in trials. Without appropriate analyses, results from cancer screening trials will be distorted.

Word count: abstract 190; text 6200.

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Appl. # 245851

Application for Funding – Budget

Funding Opportunity

Operating Grant 2011-03-01

Nominated Principal Applicant/Candidate

Last Name	First Name	Institution
HANLEY	James	McGill University/Université McGill

Financial Assistance Requested **Year** 1

Research Staff (excluding trainees)	**No.**	**Salary**	**Benefits**	**CIHR**	**Other Funding Sources**		**Total**
					Cash*	**In-Kind***	
Research Assistants	1.0	$40,000	$9,600	$49,600	$0	$0	$49,600
Technicians	0.0	$0	$0	$0	$0	$0	$0
Other personnel (as specified in Employment History)	0.0	$0	$0	$0	$0	$0	$0

Research Trainees	**No.**	**Stipend**	**Benefits**	**CIHR**	**Other Funding Sources**		**Total**
					Cash*	**In-Kind***	
Postdoctoral Fellows (post PHD, MD, etc.)	0.0	$0	$0	$0	$0	$0	$0
Graduate Students	1.0	$20,000	$3,200	$23,200	$0	$0	$23,200
Summer Students	0.0	$0	$0	$0	$0	$0	$0

Materials, Supplies and Services	**CIHR**	**Other Funding Sources**		**Total**
		Cash*	**In-Kind***	
Animals	$0	$0	$0	$0
Expendables	$2,000	$0	$0	$2,000
Services	$5,000	$0	$0	$5,000
Other (as specified in the Details of Financial Assistance Requested)	$0	$0	$0	$0

	CIHR	**Other Funding Sources**		**Total**
		Cash*	**In-Kind***	
Travel	$3,000	$0	$0	$3,000
Total Operating	$82,800	$0	$0	$82,800
Total Equipment	$1,500	$0	$0	$1,500
Total Request	$84,300	$0	$0	$84,300

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Nominated Principal Applicant/Candidate

Last Name	First Name	Institution
HANLEY	James	McGill University/Université McGill

Financial Assistance Required **Year** 2

Research Staff (excluding trainees)	**No.**	**Salary**	**Benefits**	**CIHR**	**Other Funding Sources**		**Total**
					Cash*	**In-Kind***	
Research Assistants	1.0	$40,000	$9,600	$49,600	$0	$0	$49,600
Technicians	0.0	$0	$0	$0	$0	$0	$0
Other personnel (as specified in Employment History)	0.0	$0	$0	$0	$0	$0	$0

Research Trainees	**No.**	**Stipend**	**Benefits**	**CIHR**	**Other Funding Sources**		**Total**
					Cash*	**In-Kind***	
Postdoctoral Fellows (post PHD, MD, etc.)	0.0	$0	$0	$0	$0	$0	$0
Graduate Students	1.0	$20,000	$3,200	$23,200	$0	$0	$23,200
Summer Students	0.0	$0	$0	$0	$0	$0	$0

Materials, Supplies and Services	**CIHR**	**Other Funding Sources**		**Total**
		Cash*	**In-Kind***	
Animals	$0	$0	$0	$0
Expendables	$2,000	$0	$0	$2,000
Services	$5,000	$0	$0	$5,000
Other (as specified in the Details of Financial Assistance Requested)	$0	$0	$0	$0

	CIHR	**Other Funding Sources**		**Total**
		Cash*	**In-Kind***	
Travel	$3,000	$0	$0	$3,000
Total Operating	$82,800	$0	$0	$82,800
Total Equipment	$0	$0	$0	$0
Total Request	$82,800	$0	$0	$82,800

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Appl. # 245851

Application for Funding – Budget

Funding Opportunity

Operating Grant 2011-03-01

Nominated Principal Applicant/Candidate

Last Name	First Name	Institution
HANLEY	James	McGill University/Université McGill

Financial Assistance Required **Year** 3

Research Staff (excluding trainees)	**No.**	**Salary**	**Benefits**	**CIHR**	**Other Funding Sources**		**Total**
					Cash*	**In-Kind***	
Research Assistants	1.0	$40,000	$9,600	$49,600	$0	$0	$49,600
Technicians	0.0	$0	$0	$0	$0	$0	$0
Other personnel (as specified in Employment History)	0.0	$0	$0	$0	$0	$0	$0

Research Trainees	**No.**	**Stipend**	**Benefits**	**CIHR**	**Other Funding Sources**		**Total**
					Cash*	**In-Kind***	
Postdoctoral Fellows (post PHD, MD, etc.)	0.0	$0	$0	$0	$0	$0	$0
Graduate Students	1.0	$20,000	$3,200	$23,200	$0	$0	$23,200
Summer Students	0.0	$0	$0	$0	$0	$0	$0

Materials, Supplies and Services	**CIHR**	**Other Funding Sources**		**Total**
		Cash*	**In-Kind***	
Animals	$0	$0	$0	$0
Expendables	$2,000	$0	$0	$2,000
Services	$5,000	$0	$0	$5,000
Other (as specified in the Details of Financial Assistance Requested)	$0	$0	$0	$0

	CIHR	**Other Funding Sources**		**Total**
		Cash*	**In-Kind***	
Travel	$3,000	$0	$0	$3,000
Total Operating	$82,800	$0	$0	$82,800
Total Equipment	$0	$0	$0	$0
Total Request	$82,800	$0	$0	$82,800

Human Resources

Surname	Given Names	Role	Hours / week
HANLEY	James	Nominated Principal Applicant/Ca	10
Dendukuri	Nandini	Co-Applicant	5
Liu	Zhihui	Co-Applicant	20
Strumpf	Erin	Co-Applicant	5

Budget Notes

At the moment, the minimum stipend for PhD is $17,500.
We are proposing to give a stipend of $20,000.

RA: WE are estimating this based on 2000 hours a year,
at the (minimum) McGill rate of $20/hour. WE may end up splitting
the salary over 2 persons, one more technical statistically
technical, and one more management-technical for dealing with
data-holders and arranging and co-ordinating the data-recovery.

benefits and vacation: add 24%

Service contracts are with data-holders to extract death counts
in each rectangle of Lexis space, and to produce Likelihood function
if they do not wish to disclose these counts to us.

Travel is to statistical and health service research meetings
to present methodology.

Computer is for RA.

Canadian Institutes of Health Research / Instituts de recherche en santé du Canada

PROTECTED WHEN COMPLETED

Personal Identification Number (P.I.N.)

21088

CV Module

This page is for CIHR use only. It will not be included in the evaluation of your application for funding.

Family Name	Given Name	Middle Initial(s)
Hanley	James	A

Have you previously applied to CIHR for funding? Yes [X] No [ ]

Previous family name used

Previous given name used

Title: Dr. [X] Mr. [ ] Mrs. [ ] Ms. [ ] Prof. [ ]

Courier Address
(If different from mailing address)

McGill University
Department of Epidemiology
and Biostatistics
1020 Pine Avenue West
Montreal, Québec
CANADA (H3A 1A2)

Temporary Address

Start Date
End Date

Primary Affilliation Name

McGill University

Start Date 09/1996

Primary Affiliation Address

McGill University
Epidemiology, Biostatistics, Occ health
1020 Pine Ave West
Montréal, Québec
CANADA (H3A 1A2)

Contact numbers

Phone

Primary (514) 398-6270
McGill University

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Start Date End Date

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Start Date End Date

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Web page address
http://www.epi.mcgill.ca/hanley/

Citizenship

Canadian [X] Other [ ]

Other Country of Citizenship

Permanent Residence in Canada

Permanent Resident [ ] Date of permanent residency status DD/MM/YYYY

Have you applied for permanent residency? Yes [ ] No [X]

Correspondence Language

English [X] French [ ]

Gender

Male [X] Female [ ]

Date of Birth (DD/MM/YYYY)

05/06/1947

Language	Read	Write	Speak	Understand
English (Yes or No)	YES	YES	YES	YES
French (Yes or No)	YES	NO	YES	YES

Other Languages:

Expertise

List up to ten (10) key words that best describe your expertise in research, instruments and technique.

biostatistics	
statistical methods	
epidemiologic methods	

Indicate and rank the disciplines that best correspond to your research interests. No additional pages may be added.

	Discipline		Sub Discipline	
Rank	**Code**	**Description**	**Code**	**Description**
1.	105	STATISTICS AND PROBABILITY	133	Biostatistics
2.	31	EPIDEMIOLOGY	758	Epidemiological Methods
3.				
4.				
5.				
6.				
7.				
8.				
9.				
10.				
11.				
12.				
13.				
14.				
15.				

Academic Background - One additional page may be added

Indicate all university degrees obtained and those in progress (where applicable) starting with the most recent. If you hold a co-degree from more than one institution (e.g. under the Soutien aux cotutelles de these de doctorat agreement between Quebec and France) enter each institution separately. Do not enter honorary degrees here, they should be listed in the Distinctions section.

Also indicate research training, such as postdoctoral or fellowship training. Trainees only: also list undergraduate and graduate research training experience.

Degree Type	Degree Name and Specialty	Institution/Organization and Country	Supervisor name	Start date (MM/YYYY)	Date received or expected (MM/YYYY)
Doctorate (PhD)	Doctor of Philosophy Statistics/Biometry	University of Waterloo CANADA	W.F. Forbes	09/1969	02/1973
Master's	Master's of Science Mathematics and Statistics	National University of Ireland, Cork IRELAND	-	10/1968	09/1969
Bachelor's	Bachelor's of Science Mathematics and Statistics	National University of Ireland, Cork IRELAND	-	10/1965	09/1968

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Work Experience

Starting with the most recent, indicate your current position, where applicable, and other academic and non-academic position(s) since the beginning of your university studies. For your current positions leave the end date blank. Additional pages will be accepted.

Position	Institution/Organization and Country	Department/Division and Faculty/School	Start Date (MM/YYYY)	End Date (MM/YYYY)
Full Professor	McGill University CANADA	Epidemiology and Biostatistics	09/1996	06/2012
Scientist	Royal Victoria Hospital CANADA	Clinical Epidemiology	05/1995	06/2012
Associate Professor	McGill University CANADA	Epidemiology and Biostatistics	09/1980	05/1996
Visiting Professor	Addis Ababa University ETHIOPIA	Department of Community Health	09/1992	08/1993
Consultant	World Health Organization SWITZERLAND	Cancer Unit (on sabbatic leave from McGill University)	09/1985	08/1986
Assistant Professor	Harvard School of Public Health UNITED STATES	Biostatistics	09/1977	08/1980
Assistant Scientist	Dana Farber Cancer Institute UNITED STATES	Epidemiology and Biostatistics	09/1977	08/1980
Assistant Professor	SUNY at Buffalo UNITED STATES	Statistical Science	03/1973	08/1977

Distinctions / Awards / Credentials

Starting with the most recent, indicate any recognitions received, including awards, fellowships, scholarships, licenses, qualifications, professional designation or credentials. Do not include Academic Appointments here, as they are detailed under Work Experience. Maximum 20 entries.

Name/Title and Type	Institution/Organization and Country	Effective Date (MM/YYYY)	End Date (MM/YYYY)	Specialty	Total Amount
Associate Editor Distinction	Biometrics CANADA	06/2006	06/2008		
Statistical Consultant Distinction	Hypertension	2005	2007		
Associate editor for Biostatistics Distinction	CMAJ	1998	2001		
Editorial Board Distinction	Statistics in Medicine	1996	2001		

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Patents and Intellectual Property Rights

Record the total numbers of patents / copyrights in the following table.

OBTAINED			APPLICATIONS UNDER PROCESS			TOTAL PATENTS AND INTELLECTUAL PROPERTY RIGHTS
Total individual	Total collective	Sub-total	Total individual	Total collective	Sub-total	
0	0	0	0	0	0	0

PUBLICATIONS AND PRESENTATIONS

Give the number of publications and presentations in the course of your career. Detailed information should be attached as specified in the "Contributions - details" section.

Publications	Refereed Articles	Books and Monographs	Proceedings / Book Chapters / Contributions to a collective work	Abstracts / Notes	TOTALS
Already Published	230	0	0	0	230
Accepted or in the Press	1	0	0	0	1
					231

Invited presentations	50

LITERARY AND ARTISTIC WORKS

Provide the number of literary and artistic works created in the course of your career. Detailed information should be attached as specified in the "Contributions - details" section.

IN CIRCULATION			IN PROGRESS			TOTAL LITERARY AND ARTISTIC WORKS
Total individual	Total collective	Sub-total	Total individual	Total collective	Sub-total	
0	0	0	0	0	0	0

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Supervisory Experience: To be completed by applicants requesting research trainees as part of their budget, salary support candidates and proposed supervisors of trainees.

Indicate the number of graduate students and postdoctoral fellows that you currently supervise or co-supervise. CIHR defines supervisory experience as the formal supervision or co-supervision of trainees. Enter zero (0) if not applicable.

Master 0 Doctoral 2 Post-Doctoral 0

Complete this form by listing the trainees that you have supervised/co-supervised (and are currently supervising/co-supervising) within the last five (5) years. Additional pages may be added if necessary.
* Flag those where you were/are the Primary Supervisor.

*	Name of Student	Program Type	Dates		Degree received or expected	Year Degree Rec'd (YYYY)	Research Project (Short title)	Current position and Institution
			Support Period From (MM/YY	To (MM/YYYY)				
*	LIU, Zhihui	Graduate Student	09/2010		Doctorate (PhD)		Statistical methods for Evaluating Cancer Screening	
	CHIOLERO, Arnaud	Graduate Student	09/2007		Doctorate (PhD)		Blood Pressure in Youth	Prof, U. Lausanne
	TELTSCH, Dana	Graduate Student	09/2004	05/2011	Doctorate (PhD)	2011	Reducing the development of antibiotic resistance use computer-aided improved prescribing. (co-supervisor with Robyn Tamblyn)	post-doctoral, Boston
	BEAUCHAMP, Marie-Ève	Graduate Student	09/2004	12/2009	Doctorate (PhD)	2010	Modelling of heterogeneity of proportions with correlated binary outcome data (co-supervisor with Robert Platt)	Research Associate, McGill University
	MALO, Nathalie	Graduate Student	09/2004	09/2006	Doctorate (PhD)	2006	Better statistical methods for the analysis of high-throughput data. (co-supervisor with Robert Nadon)	Postdoctoral Fellow, Uni. of San Diego
*	BELERA, Carine	Graduate Student	09/2002	03/2006	Doctorate (PhD)	2006	The ASTRO rule for biochemical (PSA) failure following treatment for prostate cancer	Statistician, Institut Bergonie

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Funds REQUESTED

List all sources of support applied for (including CIHR) as an applicant or as a co-applicant. Include the principal applicant's name, title of the proposal, funding source, program name, total amount requested (in Canadian dollars) and the period of the support. Indicate your role in the funding (principal applicant/project leader or co-applicant).

Title of Proposal		
Funding Source	**Program Name**	
Principal Applicant / Project Leader	**Your Role**	
Total Amount (CAN$)	**Support Period From (MM/YYYY)**	**To (MM/YYYY)**

Title of Proposal		
Funding Source	**Program Name**	
Principal Applicant / Project Leader	**Your Role**	
Total Amount (CAN$)	**Support Period From (MM/YYYY)**	**To (MM/YYYY)**

Title of Proposal		
Funding Source	**Program Name**	
Principal Applicant / Project Leader	**Your Role**	
Total Amount (CAN$)	**Support Period From (MM/YYYY)**	**To (MM/YYYY)**

Title of Proposal		
Funding Source	**Program Name**	
Principal Applicant / Project Leader	**Your Role**	
Total Amount (CAN$)	**Support Period From (MM/YYYY)**	**To (MM/YYYY)**

Funds CURRENTLY HELD

List all sources of support currently held (including CIHR) as an applicant or as a co-applicant. Include the principal applicant's name, title of the proposal, funding source, program name, total amount awarded (in Canadian dollars) and the period of the support. Indicate your role in the funding (principal applicant/project leader or co-applicant).

Title of Proposal Improving Patient Safety and Chronic Disease Management with a New Generation of Health Information Technologies		
Funding Source Canadian Institutes of Health Research (CIHR)	**Program Name** CIHR - Emerging Team Grant	
Principal Applicant / Project Leader Tamblyn, Robyn	**Your Role** Co-Applicant	
Total Amount (CAN$) $1,498,085	**Support Period From (MM/YYYY)** 12/2008	**To (MM/YYYY)** 11/2013

Title of Proposal HPV infection and transmission among couples through heterosexual activity (the HITCH cohort)		
Funding Source Canadian Institutes of Health Research (CIHR)	**Program Name** Operating Grant	
Principal Applicant / Project Leader Franco, E.	**Your Role** Co-Applicant	
Total Amount (CAN$) $771,968	**Support Period From (MM/YYYY)** 10/2004	**To (MM/YYYY)** 09/2013

Title of Proposal A Novel Method for Pharmacosurveillance: Combining an Electronic Prescribing and Drug Management System and Administrative Database		
Funding Source Canadian Institutes of Health Research (CIHR)	**Program Name** Operating Grand	
Principal Applicant / Project Leader Tamblyn, Robyn M.	**Your Role** Co-Applicant	
Total Amount (CAN$) $176,434	**Support Period From (MM/YYYY)** 04/2009	**To (MM/YYYY)** 09/2012

Title of Proposal Statistical methods for assessing diagnostic tests & estimating individualized probabilities of therapeutic benefit		
Funding Source Natural Sciences and Engineering Research Council of Canada (NSERC)	**Program Name**	
Principal Applicant / Project Leader	**Your Role** Principal Applicant	
Total Amount (CAN$) $60,000	**Support Period From (MM/YYYY)** 04/2007	**To (MM/YYYY)** 03/2012

Funds CURRENTLY HELD

List all sources of support currently held (including CIHR) as an applicant or as a co-applicant. Include the principal applicant's name, title of the proposal, funding source, program name, total amount awarded (in Canadian dollars) and the period of the support. Indicate your role in the funding (principal applicant/project leader or co-applicant).

Title of Proposal Long-term follow-up of the nicotine dependence in teens (NDIT) cohort		
Funding Source National Cancer Institute of Canada (NCIC)	**Program Name**	
Principal Applicant / Project Leader O'Loughlin, Jennifer	**Your Role** Co-Applicant	
Total Amount (CAN$) $1,103,901	**Support Period From (MM/YYYY)** 07/2006	**To (MM/YYYY)** 06/2011

Title of Proposal Longitudinal analysis of the Quebec birth cohort: Pathways between early childhood poverty, stress, child health, cardiovascular risk factors and associated secular trends, and resiliency		
Funding Source Canadian Institutes of Health Research (CIHR)	**Program Name** Subvention de fonctionnement Renouvellement d'une subv.	
Principal Applicant / Project Leader Seguin, Louise	**Your Role** Co-Applicant	
Total Amount (CAN$) $1,380,195	**Support Period From (MM/YYYY)** 04/2004	**To (MM/YYYY)** 06/2011

Title of Proposal		
Funding Source	**Program Name**	
Principal Applicant / Project Leader	**Your Role**	
Total Amount (CAN$)	**Support Period From (MM/YYYY)**	**To (MM/YYYY)**

Title of Proposal		
Funding Source	**Program Name**	
Principal Applicant / Project Leader	**Your Role**	
Total Amount (CAN$)	**Support Period From (MM/YYYY)**	**To (MM/YYYY)**

Funds HELD IN THE LAST FIVE YEARS

List all sources of support held in the last five years (including CIHR) as an applicant or as a co-applicant. Include the principal applicant's name, title of the proposal, funding source, program name, total amount awarded (in Canadian dollars) and the period of the support. Indicate your role in the funding (principal applicant/project leader or co-applicant).

Title of Proposal Long term graft and patient outcomes in young renal transplant recipients		
Funding Source Canadian Institutes of Health Research (CIHR)	**Program Name**	
Principal Applicant / Project Leader Foster, B.	**Your Role** Co-Applicant	
Total Amount (CAN$) $147,300	**Support Period From (MM/YYYY)** 07/2007	**To (MM/YYYY)** 06/2010

Title of Proposal The effect of warfarin use on the risk of prostate cancer death.		
Funding Source Canadian Institutes of Health Research (CIHR)	**Program Name**	
Principal Applicant / Project Leader Tagalakis, Vicky	**Your Role** Co-Applicant	
Total Amount (CAN$) $126,239	**Support Period From (MM/YYYY)** 01/2008	**To (MM/YYYY)** 03/2010

Title of Proposal Impact of technology enabled knowledge translation: Validity of a new assessment method		
Funding Source Canadian Institutes of Health Research (CIHR)	**Program Name**	
Principal Applicant / Project Leader GRAD, Roland M & PLUYE, Pierre	**Your Role** Co-Applicant	
Total Amount (CAN$) $217,575	**Support Period From (MM/YYYY)** 07/2007	**To (MM/YYYY)** 12/2009

Title of Proposal Obesity, cardiovascular risk factors and nutrition in children and adolescents.		
Funding Source Canadian Institutes of Health Research (CIHR)	**Program Name**	
Principal Applicant / Project Leader LAMBERT, Marie	**Your Role** Co-Applicant	
Total Amount (CAN$) $134,220	**Support Period From (MM/YYYY)** 05/2007	**To (MM/YYYY)** 05/2009

Funds HELD IN THE LAST FIVE YEARS

List all sources of support held in the last five years (including CIHR) as an applicant or as a co-applicant. Include the principal applicant's name, title of the proposal, funding source, program name, total amount awarded (in Canadian dollars) and the period of the support. Indicate your role in the funding (principal applicant/project leader or co-applicant).

Title of Proposal Familial study on the prevention of cardiovascular disease and type 2 diabetes in children and adolescents.		
Funding Source Canadian Institutes of Health Research (CIHR)	**Program Name**	
Principal Applicant / Project Leader Lambert, Marie	**Your Role** Co-Applicant	
Total Amount (CAN$) $824,331	**Support Period From (MM/YYYY)** 04/2004	**To (MM/YYYY)** 03/2009

Title of Proposal Familial study on the prevention of cardiovascular disease and type 2 diabetes in children and adolescents.		
Funding Source Heart and Stroke Foundation of Canada (HSFC)	**Program Name** Obesity & Health Body Weight New Emerging Team	
Principal Applicant / Project Leader Lambert, Marie	**Your Role** Co-Applicant	
Total Amount (CAN$) $500,000	**Support Period From (MM/YYYY)** 04/2004	**To (MM/YYYY)** 03/2009

Title of Proposal Pattern of care during the last six months of life of patients dying of cancer: A study using administrative database		
Funding Source Canadian Institutes of Health Research (CIHR)	**Program Name**	
Principal Applicant / Project Leader Gagnon, B.	**Your Role** Co-Applicant	
Total Amount (CAN$) $400,747	**Support Period From (MM/YYYY)** 03/2004	**To (MM/YYYY)** 04/2008

Title of Proposal Fitness Intervention trial post-stroke (FITS): Enhancing walking using home rehabilitation programs		
Funding Source Canadian Institutes of Health Research (CIHR)	**Program Name**	
Principal Applicant / Project Leader Mayo, N.	**Your Role** Co-Applicant	
Total Amount (CAN$) $822,800	**Support Period From (MM/YYYY)** 04/2004	**To (MM/YYYY)** 03/2008

Funds HELD IN THE LAST FIVE YEARS

List all sources of support held in the last five years (including CIHR) as an applicant or as a co-applicant. Include the principal applicant's name, title of the proposal, funding source, program name, total amount awarded (in Canadian dollars) and the period of the support. Indicate your role in the funding (principal applicant/project leader or co-applicant).

Title of Proposal Biostatistical methods for the analysis of follow-up data		
Funding Source Natural Sciences and Engineering Research Council of Canada (NSERC)	**Program Name**	
Principal Applicant / Project Leader Hanley, J.A.	**Your Role** Principal Applicant	
Total Amount (CAN$) $50,000	**Support Period From (MM/YYYY)** 04/2003	**To (MM/YYYY)** 03/2007

Title of Proposal Obesity and cardiovascular risk factors in children and adolescents		
Funding Source Canadian Institutes of Health Research (CIHR)	**Program Name**	
Principal Applicant / Project Leader Lambert, Marie	**Your Role** Co-Applicant	
Total Amount (CAN$) $184,562	**Support Period From (MM/YYYY)** 10/2004	**To (MM/YYYY)** 09/2006

Title of Proposal Estimating age-, gender- and risk factor-specific incidence rates of stroke and heart disease using longitudinal cohorts created from linkage of survey and administrative databases.		
Funding Source Canadian Institutes of Health Research (CIHR)	**Program Name**	
Principal Applicant / Project Leader Mayo, N.	**Your Role** Co-Applicant	
Total Amount (CAN$) $385,000	**Support Period From (MM/YYYY)** 10/2003	**To (MM/YYYY)** 09/2006

Title of Proposal		
Funding Source	**Program Name**	
Principal Applicant / Project Leader	**Your Role**	
Total Amount (CAN$)	**Support Period From (MM/YYYY)**	**To (MM/YYYY)**

NAME: HANLEY, James	PIN: 21088

Most Significant Contributions

1. Hanley JA and McNeil BJ. The meaning and use of the area under a receiver operating characteristic (ROC) curve. Radiology 1982 Apr; 143(1):29-36.

   This paper, the first in a series of several contributions on R.O.C. methods, explained the statistical behaviour of the area under the R.O.C. curve. It has been cited several thousand times since then.

2. Albertsen PC, Hanley JA, Gleason DF, Barry MJ. Competing risk analysis of men aged 55 to 74 years at diagnosis managed conservatively for clinically localized prostate cancer. JAMA. 1998 Sep 16;280(11):975-80.

   First article to make results of competing risk analyses visually obvious to physicians and patients.

3. Hanley JA. Measuring mortality reductions in cancer screening trials Accepted for publication *in Epidemiologic Reviews 2011 Theme Issue on Screening.* To appear Summer 2011.

   Third article on the appropriate way to analyze data from RCT's (and other studies) of screening for cancer. Others were in AJE in 2005, and J Medical Screening in 2010. *These articles, and the inadequacies they find in the current way of doing data analysis, are the primary motivation for this grant application.*

4. Hanley JA, Csizmadi I, Collet JP. Two-stage case-control studies: precision of parameter estimates and considerations in selecting sample size. Am J Epidemiol. 2005 Dec 15;162(12):1225-34. Epub 2005 Nov 3.

   The third in a sequence. Theoretical and practical sample size considerations for users planning to use this design. Fills a major gap, and removes a serious impediment to use of this design.

5. Hanley JA, Parnes MN. Nonparametric estimation of a multivariate distribution in the presence of censoring. Biometrics. 1983 Mar;39(1):129-39.

   One of the first to propose nonparametric estimation of a multivariate survival distribution. Area is now active research area.

NAME: HANLEY, James	PIN: 21088

Activities/Contributions (e.g. committee memberships, editorships and consultancies)

2006-2008	Associate Editor, Biometrics.
2002-2006	Chair, Local Organizing Committee (and member of Scientific Program Committee), International Biometrics Conference, Montreal 2006
1998-2001	Associate editor for biostatistics, Canadian Medical Association Journal:
1996-	Editorial Board, Statistics in Medicine
1989-	Editorial Board, Chronic Diseases in Canada
1993-	Member, NHRDP Personnel Awards (Postdoctoral / Scholar / Scientist)
1988-92	Member, Epidemiology and Disease Control Study Section (NIH)
1987-91	Ad hoc member, Diagnostic Radiology Study Section (NIH)
1988	Member, Rehabiliatation Grant Review Committee (Health and Welfare Canada)
1979-83	Member, Cancer Clinical Investigation Review Committee (NIH)
1992-95	Consultant, Conseil d'évaluation des technologies de la santé du Québec
1985-86	Consultant, Cancer Unit, World Health Organization, Geneva (on sabbatic leave)

NAME: HANLEY, James	PIN: 21088

Publications 2005-2011

(* = trainee)

2011

Teltsch DY*, Hanley J, Loo V, Goldberg P, Gursahaney A, Buckeridge DL. Infection acquisition following intensive care unit room privatization. Arch Intern Med. 2011 Jan 10;171(1):32-8.

Hanley JA. Measuring mortality reductions in cancer screening trials Accepted for publication *in Epidemiologic Reviews 2011 Theme Issue on Screening.* To appear Summer 2011.

2010

Hanley JA. Mortality reductions produced by sustained prostate cancer screening have been underestimated. J Med Screen. 2010;17(3):147-51.

Schneider-Lindner V, Quach C, Hanley JA, Suissa S. Secular trends of antibacterial prescribing in UK paediatric primary care. J Antimicrob Chemother. 2010 Dec 10. [Epub ahead of print]

Buckeridge D, Huang A, Hanley J, Kelome A, Reidel K, Verma A, Winslade N, Tamblyn R. Risk of injury associated with opioid use in older adults. J Am Geriatr Soc. 2010 Sep;58(9):1664-70.

Malo N*, Hanley JA, Carlile G, Liu J, Pelletier J, Thomas D, Nadon R. Experimental design and statistical methods for improved hit detection in high-throughput screening. J Biomol Screen. 2010 Sep;15(8):990-1000.

Szeto C*, Kost K, Hanley JA, Roy A, Christou N. A simple method to predict pretracheal tissue thickness to prevent accidental decannulation in the obese. Otolaryngol Head Neck Surg. 2010 Aug;143(2):223-9.

Eguale T, Winslade N, Hanley JA, Buckeridge DL, Tamblyn R. Enhancing pharmacosurveillance with systematic collection of treatment indication in electronic prescribing: a validation study in Canada. Drug Saf. 2010 Jul 1;33(7):559-67.

Hutcheon JA, Chiolero A*, Hanley JA. Random measurement error and regression dilution bias. BMJ. 2010 Jun 23;340:c2289.

Kidman R, Hanley JA, Subramanian SV, Foster G, Heymann J. AIDS in the family and community: The impact on child health in Malawi. *Soc Sci Med*. 2010 Jun 4. [Epub ahead of print]

Hanley J and Turner E*. Age in medieval plagues and pandemics: Dances of Death or Pearson's bridge of life? Significance, volume 7 issue 2, June 2010, p 85-87. published online: May 18 2010.

Turner EL* and Hanley JA Cultural imagery and statistical models of the force of mortality: Addison, Gompertz and Pearson. J. R. Statist. Soc. A (2010) 173, Part 3, pp. 483-499.

Publications 2005-2011

St Germaine CG, Bogaty P, Boyer L, Hanley J, Engert JC, Brophy JM. Genetic polymorphisms and the cardiovascular risk of non-steroidal anti-inflammatory drugs. Am J Cardiol. 2010 Jun 15;105(12):1740-5.

Lévesque LE, Hanley JA, Kezouh A, Suissa S. Problem of immortal time bias in cohort studies: example using statins for preventing progression of diabetes. BMJ. 2010 Mar 12;340:b5087.

Hamlin-Douglas LK, Coutlée F, Roger M, Hanley J, Franco EL, Brassard P. Determinants of human papillomavirus infection among inuit women of northern Quebec, Canada. Sex Transm Dis. 2010 Jun;37(6):377-81.

Tamblyn R, Abrahamowicz M, Dauphinee D, Wenghofer E, Jacques A, Klass D, Smee S, Eguale T, Winslade N, Girard N, Bartman I, Buckeridge DL, Hanley JA. Influence of physicians' management and communication ability on patients' persistence with antihypertensive medication. Arch Intern Med. 2010 Jun 28;170(12):1064-72.

Hanley JA, Hutcheon JA. Does children's energy intake at one meal influence their intake at subsequent meals? Or do we just think it does? Paediatr Perinat Epidemiol. 2010 May;24(3):241-8.

Maximova K, O'Loughlin J, Paradis G, Hanley JA, Lynch J. Changes in anthropometric characteristics and blood pressure during adolescence. Epidemiology. 2010 May;21(3):324-31.

Moore L*, Hanley JA, Turgeon AF, Lavoie A, Eric B. A new method for evaluating trauma centre outcome performance: TRAM-adjusted mortality estimates. Ann Surg. 2010 May;251(5):952-8.

Moore L*, Hanley JA, Turgeon AF, Lavoie A. Evaluation of the Long-term Trend in Mortality from Injury in a Mature Inclusive Trauma System. World J Surg. 2010 Apr 23. [Epub ahead of print]

Moore L*, Hanley JA, Turgeon AF, Lavoie A. Evaluating the Performance of Trauma Centers: Hierarchical Modeling Should be Used. J Trauma. 2010 Apr 16. [Epub ahead of print]

Schieir O, Thombs BD, Hudson M, Boivin JF, Steele R, Bernatsky S, Hanley J, Baron M; Canadian Scleroderma Research Group. Prevalence, severity, and clinical correlates of pain in patients with systemic sclerosis. Arthritis Care Res (Hoboken). 2010 Mar;62(3):409-17.

Burchell AN, Tellier PP, Hanley J, Coutlée F, Franco EL. Human papillomavirus infections among couples in new sexual relationships. Epidemiology. 2010 Jan;21(1):31-7.

Burchell AN, Tellier PP, Hanley J, Coutlée F, Franco EL. Influence of partner's infection status on prevalent human papillomavirus among persons with a new sex partner. Sex Transm Dis. 2010 Jan;37(1):34-40.

2009

Moore L*, Hanley JA, Lavoie A, Turgeon A. Evaluating the validity of multiple imputation for missing physiological data in the national trauma data bank. J Emerg Trauma Shock. 2009 May;2(2):73-9.

Shrier I, Steele RJ, Hanley J, Rich B. Analyses of injury count data: some do's and don'ts. Am J Epidemiol. 2009 Nov 15;170(10):1307-15. Epub 2009 Oct 7.

Bélanger M, Gray-Donald K, O'Loughlin J, Paradis G, Hanley J. When adolescents drop the ball: sustainability of physical activity in youth. Am J Prev Med. 2009 Jul;37(1):41-9.

Bellera CA*, Hanley JA, Joseph L, Albertsen PC. A statistical evaluation of rules for biochemical failure after radiotherapy in men treated for prostate cancer. Int J Radiat Oncol Biol Phys. 2009 Dec 1;75(5):1357-63. Epub 2009 Apr 22.

Maximova K, O'Loughlin J, Paradis G, Hanley JA, Lynch J. Declines in physical activity and higher systolic blood pressure in adolescence. Am J Epidemiol. 2009 Nov 1;170(9):1084-94. Epub 2009 Sep 24.

Moore L*, Hanley JA, Turgeon AF, Lavoie A, Emond M. A multiple imputation model for imputing missing physiologic data in the national trauma data bank. J Am Coll Surg. 2009 Nov;209(5):572-9. Epub 2009 Sep 17.

Shrier I, Meeuwisse WH, Matheson GO, Wingfield K, Steele RJ, Prince F, Hanley J, Montanaro M. Injury patterns and injury rates in the circus arts: an analysis of 5 years of data from Cirque du Soleil. Am J Sports Med. 2009 Jun;37(6):1143-9. Epub 2009 Mar 13.

Parent N*, Hanley JA. Assessing quality of reports on randomized clinical trials in nursing journals. Can J Cardiovasc Nurs. 2009;19(2):25-39.

Pauly RP*, Asad RA, Hanley JA, Pierratos A, Zaltzman J, Chery A, Chan CT. Long-term clinical outcomes of nocturnal hemodialysis patients compared with conventional hemodialysis patients post-renal transplantation. Clinical Transplantation 2009 Jan;23(1):47-55. Epub 2008 Sep 11.

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2008

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Publications 2005-2011

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2007

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2006

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2005

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NAME: HANLEY, James	PIN: 21088

Publications 2005-2011

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Canadian Institutes of Health Research / Instituts de recherche en santé du Canada

PROTECTED WHEN COMPLETED

Personal Identification Number (P.I.N.)

113827

CV Module

This page is for CIHR use only. It will not be included in the evaluation of your application for funding.

Family Name	Given Name	Middle Initial(s)
Dendukuri	Nandini	

Have you previously applied to CIHR for funding? Yes [X] No [ ]

Previous family name used

Previous given name used

Title: Dr. [X] Mr. [ ] Mrs. [ ] Ms. [ ] Prof. [ ]

Courier Address
(If different from mailing address)

Unité d'évaluation des technologies
Hôpital Royal Victoria - Pavillon Ross
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687 av Pins ouest
Montreal, Québec
CANADA (H3A 1A1)

Temporary Address

Start Date
End Date

Primary Affilliation Name

McGill University

Start Date 12/2003

Primary Affiliation Address

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Montreal, Québec
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Primary (514) 843-1493

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Start Date End Date

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Web page address

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Citizenship

Canadian [X] Other [ ]

Other Country of Citizenship

Permanent Residence in Canada

Permanent Resident [ ] Date of permanent residency status DD/MM/YYYY

Have you applied for permanent residency? Yes [ ] No [ ]

Correspondence Language

English [X] French [ ]

Gender	Date of Birth (DD/MM/YYYY)
Male [ ] Female [X]	17/08/1972

Language	Read	Write	Speak	Understand
English (Yes or No)	YES	YES	YES	YES
French (Yes or No)	YES	YES	YES	YES

Other Languages: Hindi, Telugu

Expertise

List up to ten (10) key words that best describe your expertise in research, instruments and technique.

Biostatistics	Sample Size
Technology Assessment	Bayesian Inference
Latent Class Models	Non gold-standard tests
Correlated Data	Verification bias
Diagnostic Tests	Meta-analysis

Indicate and rank the disciplines that best correspond to your research interests. No additional pages may be added.

	Discipline		Sub Discipline	
Rank	**Code**	**Description**	**Code**	**Description**
1.	105	STATISTICS AND PROBABILITY	133	Biostatistics
2.	31	EPIDEMIOLOGY	758	Epidemiological Methods
3.	91	HEALTH SCIENCES, APPLIED AND HEALTH SERVICES DELIVERY	434	Health Services Evaluation
4.				
5.				
6.				
7.				
8.				
9.				
10.				
11.				
12.				
13.				
14.				
15.				

Academic Background - One additional page may be added

Indicate all university degrees obtained and those in progress (where applicable) starting with the most recent. If you hold a co-degree from more than one institution (e.g. under the Soutien aux cotutelles de these de doctorat agreement between Quebec and France) enter each institution separately. Do not enter honorary degrees here, they should be listed in the Distinctions section.

Also indicate research training, such as postdoctoral or fellowship training. Trainees only: also list undergraduate and graduate research training experience.

Degree Type	Degree Name and Specialty	Institution/Organization and Country	Supervisor name	Start date (MM/YYYY)	Date received or expected (MM/YYYY)
Postdoctorate	Postdoctorate Biostatistics	Harvard University UNITED STATES	Sharon-Lise Normand	01/1999	05/2000
Doctorate (PhD)	PhD Biostatistics	McGill University CANADA	Lawrence Joseph	09/1995	05/1998
Master's Equivalent	Master of Science (Integrated) Statistics	Indian Institute of Technology, Kanpur INDIA	G. K. Shukla	08/1990	05/1995

Work Experience

Starting with the most recent, indicate your current position, where applicable, and other academic and non-academic position(s) since the beginning of your university studies. For your current positions leave the end date blank. Additional pages will be accepted.

Position	Institution/Organization and Country	Department/Division and Faculty/School	Start Date (MM/YYYY)	End Date (MM/YYYY)
Director - MUHC Technology Assessment Unit	McGill University Health Centre CANADA	Medicine	09/2008	
Medical Scientist	McGill University Health Centre CANADA		02/2007	
Assistant Professor	McGill University CANADA	Medicine Medicine	12/2003	
Research Scientist - Technology Assessment Unit (MUHC)	McGill University Health Centre CANADA	Medicine	11/2003	
Assistant Professor	McGill University CANADA	Epidemiology and Biostatistics Medicine	06/2000	
Biostatistician	St. Mary's Hospital Center CANADA	Department of Clinical Epidemiology and Community Studies Medicine	06/2000	10/2003

Distinctions / Awards / Credentials

Starting with the most recent, indicate any recognitions received, including awards, fellowships, scholarships, licenses, qualifications, professional designation or credentials. Do not include Academic Appointments here, as they are detailed under Work Experience. Maximum 20 entries.

Name/Title and Type	Institution/Organization and Country	Effective Date (MM/YYYY)	End Date (MM/YYYY)	Specialty	Total Amount
Statistical Science Award (Theorectical Category) Research award	Centers for Disease Control UNITED STATES	01/2010			$0
Chercheur Boursier Junior II (salary award) Research award	Fonds de la Recherche en Santé du Québec (FRSQ) CANADA	2009	06/2013	Biostatistics	$286,986
Chercheurs-boursier Junior I (salary award) Research award	Fonds de la Recherche en Santé du Québec (FRSQ) CANADA	06/2003	01/2009	Biostatistics	$173,134
Max Stern Recruitment Fellowship Research award	McGill Unviersity CANADA	09/1995	08/1998	Biostatistics	$42,000
Lady Meherbai Tata Scholarship Research award	Tata INDIA	01/1995	12/1995	Biostatistics	

Patents and Intellectual Property Rights

Record the total numbers of patents / copyrights in the following table.

OBTAINED			APPLICATIONS UNDER PROCESS			TOTAL PATENTS AND INTELLECTUAL PROPERTY RIGHTS
Total individual	Total collective	Sub-total	Total individual	Total collective	Sub-total	
0	0	0	0	0	0	0

PUBLICATIONS AND PRESENTATIONS

Give the number of publications and presentations in the course of your career. Detailed information should be attached as specified in the "Contributions - details" section.

Publications	Refereed Articles	Books and Monographs	Proceedings / Book Chapters / Contributions to a collective work	Abstracts / Notes	TOTALS
Already Published	56	0	0	0	56
Accepted or in the Press	6	0	0	0	6
					62

Invited presentations	36

LITERARY AND ARTISTIC WORKS

Provide the number of literary and artistic works created in the course of your career. Detailed information should be attached as specified in the "Contributions - details" section.

IN CIRCULATION			IN PROGRESS			TOTAL LITERARY AND ARTISTIC WORKS
Total individual	Total collective	Sub-total	Total individual	Total collective	Sub-total	
0	0	0	0	0	0	0

Supervisory Experience: To be completed by applicants requesting research trainees as part of their budget, salary support candidates and proposed supervisors of trainees.

Indicate the number of graduate students and postdoctoral fellows that you currently supervise or co-supervise. CIHR defines supervisory experience as the formal supervision or co-supervision of trainees. Enter zero (0) if not applicable.

Master 1 Doctoral 4 Post-Doctoral 1

Complete this form by listing the trainees that you have supervised/co-supervised (and are currently supervising/co-supervising) within the last five (5) years. Additional pages may be added if necessary.
* Flag those where you were/are the Primary Supervisor.

*	Name of Student	Program Type	Dates		Degree received or expected	Year Degree Rec'd (YYYY)	Research Project (Short title)	Current position and Institution
			Support Period From (MM/YY	To (MM/YYYY)				
	Liu, Zhihui	Graduate Student	09/2010		Doctorate (PhD)		Methods to measure (and measures of) the (actual) mortality reductions produced by cancer screening	
*	Zhou, Yan	Postdoctoral Fellow, PhD	04/2010		Postdoctorate		Bayesian statistical methods for diagnostic studies	Post Doctoral Fellow, McGill University
	Ling, Daphne	Graduate Student	09/2008		Doctorate (PhD)		Alternative approaches to TB diagnostics research: going beyond the test accuracy paradigm	
*	Liu, Guoyuan	Graduate Student	09/2008	08/2011	Master's	2011	Influence of prior distribution on Bayesian Inference for small proportions	
	Cadieux, Geneviéve	Graduate Student	08/2006	08/2011	Doctorate (PhD)	2011	Automated syndromic surveillance: assessing and optimizing physician billing claims accuracy	
	Afilalo, Jonathan	Graduate Student	09/2007	08/2009	Master's	2009	Frailty Assessment Before Cardiac Surgery	
*	de Groot	Graduate Student	01/2009	06/2009	Doctorate (PhD)	2011	Bayesian methods for adjusting for verification bias in diagnostic studies	Graduate Student, Julius Ctr, Holland
	Blagojevic, Ana	Graduate Student	09/2005	05/2008	Master's	2008	A pharmacoepidemiology study of a potential drug interaction between atorvastatin and clopidogrel following a percutaneous coronoary intervention	Research Assistant, Queen's University

Supervisory Experience: To be completed by applicants requesting research trainees as part of their budget, salary support candidates and proposed supervisors of trainees.

Indicate the number of graduate students and postdoctoral fellows that you currently supervise or co-supervise. CIHR defines supervisory experience as the formal supervision or co-supervision of trainees. Enter zero (0) if not applicable.

Master 1 Doctoral 4 Post-Doctoral 1

Complete this form by listing the trainees that you have supervised/co-supervised (and are currently supervising/co-supervising) within the last five (5) years. Additional pages may be added if necessary.
* Flag those where you were/are the Primary Supervisor.

*	Name of Student	Program Type	Dates		Degree received or expected	Year Degree Rec'd (YYYY)	Research Project (Short title)	Current position and Institution
			Support Period From (MM/YY	To (MM/YYYY)				
*	Jordie Croteau	Graduate Student	06/2005	05/2008	Master's	2008	Bayesian meta-analysis of odds ratios	
	Ansari, Hina	Graduate Student	09/2005	08/2007	Master's	2007	Inequities in Access to Health Care by Income and Private Insurance Coverage: A Longitudinal Analysis	
*	Ying Lu		09/2004	08/2006			Adjusting for verification bias in the absence of a gold-standard test: A Bayesian analysis	

Funds REQUESTED

List all sources of support applied for (including CIHR) as an applicant or as a co-applicant. Include the principal applicant's name, title of the proposal, funding source, program name, total amount requested (in Canadian dollars) and the period of the support. Indicate your role in the funding (principal applicant/project leader or co-applicant).

Title of Proposal Bayesian methods for diagnostic studies		
Funding Source Natural Sciences and Engineering Research Council of Canada (NSERC)	**Program Name** Discovery Grant	
Principal Applicant / Project Leader	**Your Role** Principal Applicant	
Total Amount (CAN$) $282,020	**Support Period From (MM/YYYY)** 06/2011	**To (MM/YYYY)** 05/2016

Title of Proposal Methods to measure (and measures of) the (actual) mortality reductions produced by cancer screening		
Funding Source Canadian Institutes of Health Research (CIHR)	**Program Name**	
Principal Applicant / Project Leader Hanley, James	**Your Role** Co-Applicant	
Total Amount (CAN$) $270,000	**Support Period From (MM/YYYY)** 09/2011	**To (MM/YYYY)** 09/2014

Title of Proposal Statistical Methods for Meta-Analysis of Tuberculosis Diagnostic Studies		
Funding Source Canadian Institutes of Health Research (CIHR)	**Program Name**	
Principal Applicant / Project Leader	**Your Role** Principal Applicant	
Total Amount (CAN$) $352,500	**Support Period From (MM/YYYY)** 09/2011	**To (MM/YYYY)** 09/2014

Title of Proposal The long-term clinical utility and cost-effectiveness of genetic testing for clopidogrel non-responsiveness following percutaneous coronary interventions		
Funding Source Canadian Institutes of Health Research (CIHR)	**Program Name** Operating Grants	
Principal Applicant / Project Leader Brophy, James	**Your Role** Co-Applicant	
Total Amount (CAN$) $180,500	**Support Period From (MM/YYYY)** 04/2011	**To (MM/YYYY)** 03/2013

Funds CURRENTLY HELD

List all sources of support currently held (including CIHR) as an applicant or as a co-applicant. Include the principal applicant's name, title of the proposal, funding source, program name, total amount awarded (in Canadian dollars) and the period of the support. Indicate your role in the funding (principal applicant/project leader or co-applicant).

Title of Proposal Prevalence functions for setting prognosis in the neonatal intensive care unit.		
Funding Source Canadian Institutes of Health Research (CIHR)	**Program Name** CIHR Team in Maternal Infant Care - Translating Knowledge	
Principal Applicant / Project Leader Lee, Shoo K.	**Your Role** Co-Applicant	
Total Amount (CAN$) $4,902,135	**Support Period From (MM/YYYY)** 07/2008	**To (MM/YYYY)** 06/2013

Title of Proposal Tuberculosis screening of health care workers: do novel blood tests have a role?		
Funding Source Canadian Institutes of Health Research (CIHR)	**Program Name** Operating Grant	
Principal Applicant / Project Leader Pai, Madhukar	**Your Role** Co-Applicant	
Total Amount (CAN$) $336,725	**Support Period From (MM/YYYY)** 10/2009	**To (MM/YYYY)** 09/2012

Title of Proposal Novel statistical methods for tuberculosis diagnostic tests		
Funding Source Canadian Institutes of Health Research (CIHR)	**Program Name** Operating Grant	
Principal Applicant / Project Leader Dendukuri, Nandini	**Your Role** Principal Applicant	
Total Amount (CAN$) $182,977	**Support Period From (MM/YYYY)** 10/2008	**To (MM/YYYY)** 09/2011

Title of Proposal Innovative approaches for diagnosing tuberculosis in the era of HIV.		
Funding Source Canadian Institutes of Health Research (CIHR)	**Program Name** Operating Grant	
Principal Applicant / Project Leader Pai, Madhukar	**Your Role** Co-Applicant	
Total Amount (CAN$) $301,878	**Support Period From (MM/YYYY)** 10/2008	**To (MM/YYYY)** 09/2011

Funds CURRENTLY HELD

List all sources of support currently held (including CIHR) as an applicant or as a co-applicant. Include the principal applicant's name, title of the proposal, funding source, program name, total amount awarded (in Canadian dollars) and the period of the support. Indicate your role in the funding (principal applicant/project leader or co-applicant).

Title of Proposal Méthodes statistiques pour les études multiniveaux		
Funding Source Fonds Québécois de la Recherche sur la Nature et les Technologies (FQRNT)	**Program Name** Recherche en Équipe	
Principal Applicant / Project Leader Dendukuri, Nandini	**Your Role** Principal Applicant	
Total Amount (CAN$) $145,800	**Support Period From (MM/YYYY)** 05/2008	**To (MM/YYYY)** 04/2011

Title of Proposal Bayesian methods for diagnostic test studies		
Funding Source Natural Sciences and Engineering Research Council of Canada (NSERC)	**Program Name**	
Principal Applicant / Project Leader Dendukuri, Nandini	**Your Role** Principal Applicant	
Total Amount (CAN$) $45,000	**Support Period From (MM/YYYY)** 04/2006	**To (MM/YYYY)** 03/2011

Title of Proposal		
Funding Source	**Program Name**	
Principal Applicant / Project Leader	**Your Role**	
Total Amount (CAN$)	**Support Period From (MM/YYYY)**	**To (MM/YYYY)**

Title of Proposal		
Funding Source	**Program Name**	
Principal Applicant / Project Leader	**Your Role**	
Total Amount (CAN$)	**Support Period From (MM/YYYY)**	**To (MM/YYYY)**

Funds HELD IN THE LAST FIVE YEARS

List all sources of support held in the last five years (including CIHR) as an applicant or as a co-applicant. Include the principal applicant's name, title of the proposal, funding source, program name, total amount awarded (in Canadian dollars) and the period of the support. Indicate your role in the funding (principal applicant/project leader or co-applicant).

Title of Proposal A pharmacoepidemiology study of the cardiovascular safety of bisphosphonates.		
Funding Source Canadian Institutes of Health Research (CIHR)	**Program Name** Operating Grant	
Principal Applicant / Project Leader Brophy, James	**Your Role** Co-Applicant	
Total Amount (CAN$) $174,600	**Support Period From (MM/YYYY)** 04/2008	**To (MM/YYYY)** 03/2010

Title of Proposal Socioeconomic status and perinatal health		
Funding Source Canadian Institutes of Health Research (CIHR)	**Program Name** Operating Grants	
Principal Applicant / Project Leader Joseph, K.S.	**Your Role** Co-Applicant	
Total Amount (CAN$) $431,288	**Support Period From (MM/YYYY)** 04/2007	**To (MM/YYYY)** 03/2010

Title of Proposal Non-steroidal anti-inflammatory drugs & cardiovascular risk: an international patient level meta-analysis of observational studies.		
Funding Source Canadian Institutes of Health Research (CIHR)	**Program Name** Operating Grants	
Principal Applicant / Project Leader Brophy, James	**Your Role** Co-Applicant	
Total Amount (CAN$) $183,616	**Support Period From (MM/YYYY)** 10/2007	**To (MM/YYYY)** 09/2009

Title of Proposal Validation of interferon-gamma assay for the diagnosis of tuberculosis infection in health care workers.		
Funding Source Canadian Institutes of Health Research (CIHR)	**Program Name** Operating Grant	
Principal Applicant / Project Leader Pai, Madhukar	**Your Role** Co-Applicant	
Total Amount (CAN$) $249,285	**Support Period From (MM/YYYY)** 10/2006	**To (MM/YYYY)** 09/2009

Funds HELD IN THE LAST FIVE YEARS

List all sources of support held in the last five years (including CIHR) as an applicant or as a co-applicant. Include the principal applicant's name, title of the proposal, funding source, program name, total amount awarded (in Canadian dollars) and the period of the support. Indicate your role in the funding (principal applicant/project leader or co-applicant).

Title of Proposal Validation of sFAS measurement for the diagnosis of acute coronary syndrome		
Funding Source Canadian Institutes of Health Research (CIHR)	**Program Name** Proof of Principle	
Principal Applicant / Project Leader Hebert, Marie-Josée	**Your Role** Co-Applicant	
Total Amount (CAN$) $150,000	**Support Period From (MM/YYYY)** 04/2008	**To (MM/YYYY)** 03/2009

Title of Proposal Antithrombotic treatment intensity and the risk of hemorrhagic complications in the elderly: a population-based study.		
Funding Source Canadian Institutes of Health Research (CIHR)	**Program Name** Operating Grants	
Principal Applicant / Project Leader Levesque, Linda	**Your Role** Co-Applicant	
Total Amount (CAN$) $205,498	**Support Period From (MM/YYYY)** 04/2007	**To (MM/YYYY)** 03/2009

Title of Proposal Prognostic Models in Obstetrics		
Funding Source Canadian Institutes of Health Research (CIHR)	**Program Name** NSHRF/CIHR Regional Partnership	
Principal Applicant / Project Leader Allen, Victoria	**Your Role** Co-Applicant	
Total Amount (CAN$) $125,708	**Support Period From (MM/YYYY)** 10/2006	**To (MM/YYYY)** 09/2008

Title of Proposal Epidémiologie clinique et moleculaire et des facteurs virulence du clostridium difficile dans le contexte d'une éclosion récente au Québec.		
Funding Source Fonds de la Recherche en Santé du Québec (FRSQ)	**Program Name** subvention	
Principal Applicant / Project Leader Loo, Vivian	**Your Role** Co-Applicant	
Total Amount (CAN$) $1,000,000	**Support Period From (MM/YYYY)** 01/2006	**To (MM/YYYY)** 12/2007

Funds HELD IN THE LAST FIVE YEARS

List all sources of support held in the last five years (including CIHR) as an applicant or as a co-applicant. Include the principal applicant's name, title of the proposal, funding source, program name, total amount awarded (in Canadian dollars) and the period of the support. Indicate your role in the funding (principal applicant/project leader or co-applicant).

Title of Proposal		
A pharmacoepidemiology study of a potential drug interaction between atorvastatin and clopidogrel following percutaneous coronary intervention.		
Funding Source	**Program Name**	
Canadian Institutes of Health Research (CIHR)	Operating Grant	
Principal Applicant / Project Leader	**Your Role**	
Brophy, James	Co-Applicant	
Total Amount (CAN$)	**Support Period From (MM/YYYY)**	**To (MM/YYYY)**
$100,000	10/2005	09/2007

Title of Proposal		
Collaborative Development and Implementation of a Joint HTA Unit by two University Hospital Networks in Montreal, Quebec		
Funding Source	**Program Name**	
Canadian Coordinating Office for Health Technology Assessment	HTA Capacity - Building Grants Program	
Principal Applicant / Project Leader	**Your Role**	
Brophy, James	Co-Applicant	
Total Amount (CAN$)	**Support Period From (MM/YYYY)**	**To (MM/YYYY)**
$197,000	02/2005	03/2007

Title of Proposal		
Development of a user-friendly interface for statistical analysis programs for diagnostic test studies in the absence of a gold-standard.		
Funding Source	**Program Name**	
World Health Organization (WHO)	TDR (The Special programme for research and training in trop	
Principal Applicant / Project Leader	**Your Role**	
Dendukuri, Nandini	Principal Applicant	
Total Amount (CAN$)	**Support Period From (MM/YYYY)**	**To (MM/YYYY)**
$10,000	01/2006	12/2006

Title of Proposal		
Méthodes statistiques améliorées pour recherche sur les services de santé		
Funding Source	**Program Name**	
Fonds de la Recherche en Santé du Québec (FRSQ)	Infrastructure grant	
Principal Applicant / Project Leader	**Your Role**	
Dendukuri, Nandini	Principal Applicant	
Total Amount (CAN$)	**Support Period From (MM/YYYY)**	**To (MM/YYYY)**
$45,000	07/2003	06/2006

1. Most significant research contributions

My research career, currently supported by a Chercheur Boursier Junior 2 award from the Fonds de la Recherche en Santé du Québec, has focused on development of statistical methods for diagnostic studies. My research has been consistently supported by grants from Canadian organizations (NSERC, FQRNT, CIHR and FRSQ). My most significant contributions can be classified into five areas as follows:

i) ***Adjusting for imperfect reference standard:*** In the absence of a gold-standard reference test, joint models for multiple, imperfect tests are needed. To avoid bias, such models should account for dependence between tests, given the latent disease status. *Dendukuri and Joseph, Biometrics, 2001* described use of fixed or random effects models for this purpose, while *Dendukuri et al, Statistics in Medicine, 2009* proposed a multiple latent variable model to take into account the biological mechanism on which each imperfect test is based. A recently accepted paper (*Dendukuri et al, Statistics in Biopharmaceutical Research, 2010*), elucidated pitfalls associated with the simplistic composite reference approach that is widely used in the absence of a gold-standard reference. To support use of these methods I have created a number of free software packages (see Section 5.4).

ii) ***Adjusting for verification bias:*** Another common bias in diagnostic studies is verification bias. It arises when a biased sample of patients are verified by a reference test. An article based on my student's thesis (*Lu et al., Statistics in Medicine, 2010*) describes a Bayesian approach to simultaneously correct for partial verification bias and reference standard bias as well. Together with a visiting student from the Netherlands, I have also developed methods to adjust for this bias in the context of a differential verification design (*De Groot et al., Epidemiology, 2010, De Groot et al., BMJ, Submitted*).

iii) ***Diagnostic meta-analysis:*** With the increasing interest in evidence-based medical practice there is a move to summarize information across clinical studies. I developed a model for diagnostic meta-analysis that corrects for verification bias (*Dendukuri et al., CMAJ, 2007, De Groot et al., submitted to Am J Epi*). A recently completed project describes meta-analysis in the absence of a gold-standard (*Dendukuri et al., Biometrics submitted*) with an accompanying software package (HSROC in 5.4).

iv) ***Sample size for diagnostic tests*****:** I have worked on the problem of designing diagnostic studies in the absence of a gold-standard test (*Dendukuri et al, Biometrics 2004*, *Dendukuri et al. Statistics in Medicine, 2010*). Our work highlights the need for realistic modeling of results from such studies, failing which studies can be arbitrarily small leading to imprecise and potentially biased results.

v) ***Statistical applications in epidemiology and health technology assessment*****:** Alongside my research I have continually worked on inter-disciplinary projects, principally in epidemiology and in health technology assessment. I participate in projects requiring complicated modeling, e.g. hierarchical models (*Cole et al., Am J Psy, 2003, Oughton et al. Infect. Contr Hosp Epi, 2009*), Bayesian analysis (*Christopher et al, PLOS One, 2010*) or competing risks analysis (S1). Health technology assessment reports I have authored (see 5.3). These reports are aimed at helping the McGill University Health Centre make cost-effective decisions. They are accessed by readers world-wide (over 200,000 hits annually). Besides serving to support my colleagues, my involvement in these projects provides motivating examples for my methodological research projects. These projects also help to enrich my teaching. Over the last decade I have come to value my ability to straddle methodological and applied research areas as a unique asset. I have also tried to inculcate this attitude in my students/trainees.

2. Activities and Contributions (Selected)

Committees (Outside McGill University)

Member, Diagnostics Expert Evaluation Panel (DEEP), TDR/WHO 2006-2007

Peer Review Panel Member:

Population Health, Canadian Institutes of Health Research (CIHR), October 2009
Committee Clinique et Radiologie, Fonds de la Recherche en Santé du Québec (FRSQ) 2010-2012

Consulting

Director, Technology Assessment Unit, McGill University Health Centre, 2008-Present

Representative Invited presentations during 2006-2010 (7/19)

- Bayesian approach to adjusting for partial and differential verification bias. Centre for Clinical Epidemiology and Community Studies, Jewish General Hospital, **Montreal**, 2010
- Bayesian sample size determination for prevalence and diagnostic test studies in the absence of a gold standard test. Département de mathématique et statistique, Université Laval, **Québec,** 2009
- Estimation of latent TB infection prevalence using mixture models. Respiratory Epidemiology and Clinical Research Unit, McGill University, **Montreal,** 2008
- BLCM: A user friendly software package for Bayesian estimation of Latent Class Models. Diagnostic Experts Evaluation Panel (DEEP) Meeting, **Geneva.** 2007
- Review of statistical methods for evaluation of diagnostic tests in the absence of a gold-standard. Diagnostic Experts Evaluation Panel (DEEP) Meeting, **Geneva.** 2006

Knowledge Translation (Teaching outside of McGill University requirements)

- Workshop on 'Bayesian Methods for Adjusting for Bias in Epidemiologic Studies' (With Invited speaker, Paul Gustafson), McGill University, 2010
- Introduction to Bayesian methods in Biostatistics, Indian Institute of Public Health, Hyderabad, India, 2009 & 2010
- Workshop on Bayesian Methods for Health Technology Assessment. Canadian Drugs and Technologies in Health, Annual Symposium, Ottawa. 2009

Journal Reviews

American Journal of Managed Care; Biometrics; Canadian Journal of Statistics; Communications in Statistics; Disease Markers and Cancer Biomarkers; Epidemiology; Internation Journal of Tuberculosis and Lung Disease; Open Medicine; Personalized Medicine; Radiology; South African Statistical Journal; Statistics in Medicine; The Lancet; The Biometrical Journal; British Medical Journal; European Respiratory Journal

Teaching at McGill University (Courses taught during 2006-2011)

513-694L: Statistial Inference II (2006) ; BIOS 602: Regression Models (2006-2010); POTH 618: An introductory course in regression analysis(2011)

Supervision (2006-2011) (Total 24)

Graduate Students 9 McGill, 2 external; Biostatistics Research Assistants 2; Technology Assessment Research Assistants 4; Summer students 6; Postdoctoral fellow 1

3. Interruptions and Delays

Maternity leave in March 1, 2004 - February 28, 2005 and again in April 1, 2007 to October 1, 2007.

4. Patents and Intellectual Property Rights

NONE

5. Publications List

(student or research assistant (bold) working under my supervision)

5.1 Selected publications appeared or accepted in peer-reviewed journals in the last 5 years (17/26)
(Applied articles listed below involved use of non-standard statistical methods such as hierarchical models, latent class models, incremental value statistics, correction for verification bias etc.)

1. **Cadieux G**, Buckeridge D, Jacques A, Libman M, Dendukuri N and Tamblyn R. Accuracy of syndrome definitions based on diagnoses in physician claims. BMC Public Health. 11:17. 2011
2. Dendukuri N, **Wang L**, Hadgu A. Evaluating diagnostic tests for *Chlamydia trachomatis* in the absence of a gold-standard: A comparison of 3 statistical methods. Accepted by Statistics in Biopharmaceutical Research (Oct 2010)
3. **DeGroot J**, Dendukuri N, Bossuyt PM, Reit sma JB, Janssen KJM, Moons KGM. Adjusting for differential verification bias in diagnostic accuracy studies: A Bayesian approach. Epidemiology, 22(2):234-41, 2011
4. **Xie X**, Dendukuri N, McGregor M. Percutaneous Radiofrequency ablation for the treatment of hepatocellular carcinoma: A Health Technology Assessment. International Journal of Technology Assessment in Health Care, 26(4): 390-397. 2010
5. Dendukuri N, Bèlisle P, Joseph L. Bayesian sample size determination for diagnostic test studies in the absence of a gold-standard test: Comparing identifiable to non-identifiable models. Statistics in Medicine, 29(26): 2688-2697. 2010.
6. **Lu Y**, Dendukuri N, **Schiller I**, Joseph L. A Bayesian approach to adjusting for verification bias in diagnostic test studies. Statistics in Medicine 29(24):2532-43. 2010
7. **Filion K**, **El-Khoury F, Bielinski M, Schiller I,** Dendukuri N, Brophy J. Omega-3 Fatty Acids In High-risk Cardiovascular Patients: A meta-analysis Of Randomized Controlled Trials.
BMC Cardiovascular Disorders, 10:24. 2010
8. **Afilalo J**, Eisenberg MJ, Morin J, Bergman H, Monette J, Noiseux N, Perrault LP, Alexander KP, Langlois Y, Dendukuri N, Chamoun P, Kasparian G, Robichaud S, Gharacholou SM, Boivin J. Gait Speed as an Incremental Predictor of Mortality and Major Morbidity in Elderly Patients Undergoing Cardiac Surgery. J Am Coll Cardiol, 56(20): 1668-1676, 2010
9. **Fontela PS**, Pai N, **Schiller I**, Dendukuri N, Ramsay A, Pai M. Quality and Reporting of Diagnostic Accuracy Studies in TB, HIV and Malaria: Evaluation Using QUADAS and STARD Standards. PLOS One, 4(11):e7753. 2009
10. Oughton M, Loo V, Dendukuri N, Fenn S, Lynch A, Libman M. Plain soap and water are superior to alcohol rub and antiseptic wipes for removal of Clostridium difficile by handwashing. Infection Control and Hospital Epidemiology 30(10):939-44.2009
11. Steingart K, Dendukuri N, Henry M, **Schiller I**, Payam N, Hopewell PC, Ramsay A, Pai M, Laal S. Bayesian meta-Analysis of randomized controlled trials examining the effect of Omega-3 fatty acids on survival and restenosis in high risk cardiovascular patients. Clinical and Vaccine Immunology. Clinical and Vaccine Immunology, 16(2):260-76. 2009
12. Dendukuri N, Hadgu A, **Wang L**. Modeling conditional dependence between diagnostic tests: A multiple latent variable model. Statistics in Medicine. 28(3):441-61. 2009
13. Hanley J, **Dendukuri N**. Efficient sampling approaches to address confounding in database studies. Statistical Methods in Medical Research, 18(1):81-105. 2008

14. Pai M, Dendukuri N, **Wang L**, Joshi R, Kalantri S, Rieder H. Improving the estimation of tuberculosis infection prevalence using T-cell-based assay and mixture models. International Journal of Tuberculosis and Lung Disease. 12(8): 895-902. 2008
15. Dendukuri N, **Chiu K**, Brophy J. Validity of Electron Beam Computed Tomography for Coronary Artery Disease: A Systematic Review and Meta-analysis. BMC Medicine. 5(1):35. 2007
16. Dendukuri N, Khetani K, **McIsaac M**, Brophy J. Testing for HER2 positive breast cancer: A systematic review and cost-effectiveness analysis. Canadian Medical Association Journal. 176(10): 1429-34. 2007
17. **Ligthart S**, **Vlemmix V**, Dendukuri N, Brophy J. The cost-effectiveness of Sirolimus eluting stents - evaluating the evaluations. Canadian Medical Association Journal,176 (2):199-205. 2007

5.2 Publications currently submitted to peer-reviewed journals (6/7)

S1. Loo V, Bourgault A-M, Poirier P, Lamothe F, Michaud S, Turgeon N, Toye B, Beaudoin A, Frost EH, Gilca R, Brassard P, Dendukuri N, Béliveau C, Oughton M, Brukner I, Dascal A. Healthcare-associated *Clostridium difficile* Infection and Colonization are Differentially Associated with Defined Host and Pathogen Variables. New England Journal of Medicine. Aug 2010
S2. Hadgu A, Dendukuri N, **Wang L**. Evaluation of Screening Tests for Chlamydia Trachomatis: Bias Associated with the Patient Infected Status Algorithm. American Journal of Epidemiology. Dec 2010
S3. **DeGroot J**, Dendukuri N, Janssen KJM, Reitsma JB, Brophy J, Joseph L, Bossuyt PM, Moons KGM. Adjusting for partial verification or work-up bias in meta-analyses of diagnostic accuracy studies. American Journal of Epidemiology. Oct 2010
S4. **DeGroot J**, Bossuyt PM, Reitsma JB, Dendukuri N, Janssen KJM, Moons KGM. Verification problems in diagnostic accuracy studies: consequences and solutions. British Medical Journal Aug 2010.
S5. René P, Frenette CP, **Schiller I**, Dendukuri N, Brassard P, Fenn S, Loo VG. Comparison of Eight Commercial Enzyme Immunoassays for the Detection of Clostridium difficile from Stool Samples. Journal of Clinical Microbiology. Sep 2010
S6. Dendukuri N, **Schiller I**, Joseph L, Pai M. Bayesian meta-analysis of a test for tuberculous pleuritis in the absence of a gold-standard reference. Biometrics. Jan 2011

5.3 Representative technology assessment reports (Non-refereed) (see complete list at http://www.mcgill.ca/tau)

1. **Xie X**, Dendukuri N, McGregor M. The use of probiotics in the prevention and treatment of Clostridium Difficile diarrhea: An Update. 2009
2. **Pan I**, Dendukuri N. Subthalamic Deep Brain Stimulation (DBS): Clinical efficacy, safety and cost compared to medical therapy for the treatment of Parkinson's Disease. 2009
3. **Xie X**, Dendukuri N, McGregor M. Radiofrequency ablation for treatment of Barrett's esophagus: A systematic review and cost analysis. 2009
4. **Pan I**, Dendukuri N, McGregor M. Efficacy and cost-effectiveness of Collatamp- G for infection prophylaxis in cardiac surgery. 2009
5. **Xie X**, Dendukuri N, McGregor M. Percutaneous Radiofrequency Ablation for treatment of hepatocellular carcinoma. 2009
6. Dendukuri N, Brophy J. Testing for HER2 positive breast cancer: A cost-effectiveness analysis. 2006

5.4 Statistical Software (Available from my webpage: http://www.nandinidendukuri.com/)

- WinBUGS programs for modeling conditional dependence between two non-gold standard diagnostic tests using fixed or random effects
- LCMR: An R library to estimate latent class models with random effects using a Bayesian approach.

- BLCM: A user-friendly program for Bayesian estimation of latent class models
- HSROC: An R library for Bayesian estimation of a hierarchical diagnostic meta-analysis model that allows for the reference standard to be perfect or imperfect.

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CV Module

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Family Name	Given Name	Middle Initial(s)
Liu	Zhihui	

Have you previously applied to CIHR for funding? Yes ☐ No ☒

Previous family name used

Previous given name used

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Biostatistics and Occupational Health
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CANADA (H3A 1A2)

Temporary Address

Start Date

End Date

Primary Affilliation Name

McGill University

Start Date 09/2010

Primary Affiliation Address

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Biostatistics and Occupational Health
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Contact numbers

Phone

Primary (514) 797-9956

Secondary

Temporary

Start Date End Date

Fax

Primary

Temporary

Start Date End Date

Electronic Addresses

E-Mail

zhihui.liu@mail.mcgill.ca

Web page address

Citizenship

Canadian ☐ Other ☒

Other Country of Citizenship CHINA

Permanent Residence in Canada

Permanent Resident ☐ Date of permanent residency status _____ DD/MM/YYYY

Have you applied for permanent residency? Yes ☐ No ☒

Correspondence Language

English ☒ French ☐

Language	Read	Write	Speak	Understand
English (Yes or No)	YES	YES	YES	YES
French (Yes or No)	NO	NO	NO	NO

Other Languages: Chinese/Mandarin

Gender

Male ☐ Female ☒

Date of Birth (DD/MM/YYYY)

26/10/1986

Expertise

List up to ten (10) key words that best describe your expertise in research, instruments and technique.

Biostatistics	

Indicate and rank the disciplines that best correspond to your research interests. No additional pages may be added.

	Discipline		Sub Discipline	
Rank	**Code**	**Description**	**Code**	**Description**
1.	105	STATISTICS AND PROBABILITY	133	Biostatistics
2.				
3.				
4.				
5.				
6.				
7.				
8.				
9.				
10.				
11.				
12.				
13.				
14.				
15.				

Academic Background - One additional page may be added

Indicate all university degrees obtained and those in progress (where applicable) starting with the most recent. If you hold a co-degree from more than one institution (e.g. under the Soutien aux cotutelles de these de doctorat agreement between Quebec and France) enter each institution separately. Do not enter honorary degrees here, they should be listed in the Distinctions section.

Also indicate research training, such as postdoctoral or fellowship training. Trainees only: also list undergraduate and graduate research training experience.

Degree Type	Degree Name and Specialty	Institution/Organization and Country	Supervisor name	Start date (MM/YYYY)	Date received or expected (MM/YYYY)
Doctorate (PhD)	Doctor of Philosophy Biostatistics	McGill University CANADA	Prof. James A. Hanley; Prof. Nandini Dendukuri	09/2010	09/2014
Master's	Master of Science Statistics	McMaster University CANADA	Prof. Peter D. M. Macdonald	09/2009	11/2010
Bachelor's, Honours	Honours Bachelor of Science Mathematics and Statistics	McMaster University CANADA	Not applicable	09/2005	06/2009

Work Experience

Starting with the most recent, indicate your current position, where applicable, and other academic and non-academic position(s) since the beginning of your university studies. For your current positions leave the end date blank. Additional pages will be accepted.

Position	Institution/Organization and Country	Department/Division and Faculty/School	Start Date (MM/YYYY)	End Date (MM/YYYY)
Research Assistant	McGill University CANADA	Epidemiology and Biostatistics	09/2010	
Research Assistant	McMaster University CANADA	Mathematics and Statistics	05/2010	08/2010
Teaching Assistant	McMaster University CANADA	Mathematics and Statistics	09/2009	08/2010

Distinctions / Awards / Credentials

Starting with the most recent, indicate any recognitions received, including awards, fellowships, scholarships, licenses, qualifications, professional designation or credentials. Do not include Academic Appointments here, as they are detailed under Work Experience. Maximum 20 entries.

Name/Title and Type	Institution/Organization and Country	Effective Date (MM/YYYY)	End Date (MM/YYYY)	Specialty	Total Amount
Associate Statistician Credential	Statistical Society of Canada CANADA	2010			
McGill Provost's Graduate Fellowship Research award	McGill University CANADA	2010	2011		$10,000
McGill International Doctoral Awards Research award	McGill University CANADA	2010	2011		$10,900
Honours B.Sc. with Distinction Distinction	McMaster University CANADA	2009			
The J. Douglas Bankier Memorial Scholarship Research award	McMaster University CANADA	2008			
McMaster Dean's Honour List Distinction	McMaster University CANADA	2008	2009		

Patents and Intellectual Property Rights

Record the total numbers of patents / copyrights in the following table.

OBTAINED			APPLICATIONS UNDER PROCESS			TOTAL PATENTS AND INTELLECTUAL PROPERTY RIGHTS
Total individual	Total collective	Sub-total	Total individual	Total collective	Sub-total	
0	1	1	0	0	0	1

PUBLICATIONS AND PRESENTATIONS

Give the number of publications and presentations in the course of your career. Detailed information should be attached as specified in the "Contributions - details" section.

Publications	Refereed Articles	Books and Monographs	Proceedings / Book Chapters / Contributions to a collective work	Abstracts / Notes	TOTALS
Already Published	0	0	0	0	0
Accepted or in the Press	0	0	1	0	1
					1

Invited presentations	2

LITERARY AND ARTISTIC WORKS

Provide the number of literary and artistic works created in the course of your career. Detailed information should be attached as specified in the "Contributions - details" section.

IN CIRCULATION			IN PROGRESS			TOTAL LITERARY AND ARTISTIC WORKS
Total individual	Total collective	Sub-total	Total individual	Total collective	Sub-total	
0	0	0	0	0	0	0

Supervisory Experience: To be completed by applicants requesting research trainees as part of their budget, salary support candidates and proposed supervisors of trainees.

Indicate the number of graduate students and postdoctoral fellows that you currently supervise or co-supervise. CIHR defines supervisory experience as the formal supervision or co-supervision of trainees. Enter zero (0) if not applicable.

Master 0 Doctoral 0 Post-Doctoral 0

Complete this form by listing the trainees that you have supervised/co-supervised (and are currently supervising/co-supervising) within the last five (5) years. Additional pages may be added if necessary.

* Flag those where you were/are the Primary Supervisor.

*	Name of Student	Program Type	Dates		Degree received or expected	Year Degree Rec'd (YYYY)	Research Project (Short title)	Current position and Institution
			Support Period From (MM/YY	To (MM/YYYY)				

Funds REQUESTED

List all sources of support applied for (including CIHR) as an applicant or as a co-applicant. Include the principal applicant's name, title of the proposal, funding source, program name, total amount requested (in Canadian dollars) and the period of the support. Indicate your role in the funding (principal applicant/project leader or co-applicant).

Title of Proposal		
Funding Source	**Program Name**	
Principal Applicant / Project Leader	**Your Role**	
Total Amount (CAN$)	**Support Period** **From (MM/YYYY)**	**To (MM/YYYY)**

Title of Proposal		
Funding Source	**Program Name**	
Principal Applicant / Project Leader	**Your Role**	
Total Amount (CAN$)	**Support Period** **From (MM/YYYY)**	**To (MM/YYYY)**

Title of Proposal		
Funding Source	**Program Name**	
Principal Applicant / Project Leader	**Your Role**	
Total Amount (CAN$)	**Support Period** **From (MM/YYYY)**	**To (MM/YYYY)**

Title of Proposal		
Funding Source	**Program Name**	
Principal Applicant / Project Leader	**Your Role**	
Total Amount (CAN$)	**Support Period** **From (MM/YYYY)**	**To (MM/YYYY)**

Funds CURRENTLY HELD

List all sources of support currently held (including CIHR) as an applicant or as a co-applicant. Include the principal applicant's name, title of the proposal, funding source, program name, total amount awarded (in Canadian dollars) and the period of the support. Indicate your role in the funding (principal applicant/project leader or co-applicant).

Title of Proposal		
Funding Source	**Program Name**	
Principal Applicant / Project Leader	**Your Role**	
Total Amount (CAN$)	**Support Period** **From (MM/YYYY)**	**To (MM/YYYY)**

Title of Proposal		
Funding Source	**Program Name**	
Principal Applicant / Project Leader	**Your Role**	
Total Amount (CAN$)	**Support Period** **From (MM/YYYY)**	**To (MM/YYYY)**

Title of Proposal		
Funding Source	**Program Name**	
Principal Applicant / Project Leader	**Your Role**	
Total Amount (CAN$)	**Support Period** **From (MM/YYYY)**	**To (MM/YYYY)**

Title of Proposal		
Funding Source	**Program Name**	
Principal Applicant / Project Leader	**Your Role**	
Total Amount (CAN$)	**Support Period** **From (MM/YYYY)**	**To (MM/YYYY)**

Funds HELD IN THE LAST FIVE YEARS

List all sources of support held in the last five years (including CIHR) as an applicant or as a co-applicant. Include the principal applicant's name, title of the proposal, funding source, program name, total amount awarded (in Canadian dollars) and the period of the support. Indicate your role in the funding (principal applicant/project leader or co-applicant).

Title of Proposal		
Funding Source	**Program Name**	
Principal Applicant / Project Leader	**Your Role**	
Total Amount (CAN$)	**Support Period From (MM/YYYY)**	**To (MM/YYYY)**

Title of Proposal		
Funding Source	**Program Name**	
Principal Applicant / Project Leader	**Your Role**	
Total Amount (CAN$)	**Support Period From (MM/YYYY)**	**To (MM/YYYY)**

Title of Proposal		
Funding Source	**Program Name**	
Principal Applicant / Project Leader	**Your Role**	
Total Amount (CAN$)	**Support Period From (MM/YYYY)**	**To (MM/YYYY)**

Title of Proposal		
Funding Source	**Program Name**	
Principal Applicant / Project Leader	**Your Role**	
Total Amount (CAN$)	**Support Period From (MM/YYYY)**	**To (MM/YYYY)**

2010- Member, Southern Ontario Regional Association of the Statistical Society of Canada
2009- Member, Statistical Society of Canada
2009- Member, American Statistical Association
2008-09, Peer Mentor, Science Peer Mentoring Program, McMaster University
2008-09, Peer Mentor, International Student Mentoring Program, McMaster University
2008-09, Mac Ambassador, Career Services, McMaster University
2007-08, Malaria Awareness Campaign leader, Red Cross Club, McMaster University

Title: Method for refining ferro nickel alloy from nickel oxide mine
Patent No. CN101418356
Filed on Oct 28, 2007
Published on Apr 29, 2009
Country of issue: State Intellectual Property Office, China
Inventors: Liu, Yunsheng, Liu, Zhihui and Liu, Yunqiang
Impact: This invention, which provides a method for extracting nickel-iron alloy from nickel oxide ore, reduces energy consumption and waste emission.

1. Accepted or in press refereed contributions (attach acceptance letters)

Liu, Z and Malik, R. (2011). Case Studies in Data Analysis: Proteomic Biomarkers for Disease Status - Contribution by Zhihui (Amy) LIU and Rajat MALIK. To appear in Canadian Journal of Statistics.

Request for Copyright Transfer
Tue, January 11, 2011 9:12:12 PM
From: Julie Falkner <jcfalkner@gmail.com>
To: amyatmac@yahoo.ca

Dear Amy Liu,

Your manuscript entitled "Contribution by Zhihui (Amy) LIU and Rajat MALIK" has been accepted for publication in The Canadian Journal of Statistics.

A signed copyright transfer agreement (which is attached) is required for publication. Please scan the completed form to PDF (ensuring that the file size is reasonable) and return it to me.

Regards,
Julie Falkner
CJS Assistant

---

2. Presentations

- Poster Presentation of Case Studies in Data Analysis: Metabolism of bradykinin and endogenous des-Arg9-bradykinin in human plasma: contribution to the pathophysiology of angiooedema associated with ACE inhibitors, 38th Annual Statistical Society of Canada Meeting, 2010

- Poster Presentation of Case Studies in Data Analysis: Proteomic Biomarkers for Disease Status, 37th Annual Statistical Society of Canada Meeting, 2009

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178795

CV Module

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Family Name	Given Name	Middle Initial(s)
Strumpf	Erin	C

Have you previously applied to CIHR for funding? Yes [X] No [ ]

Previous family name used

Previous given name used

Title: Dr. [X] Mr. [ ] Mrs. [ ] Ms. [ ] Prof. [ ]

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Pavillion Leacock 418
855 rue Sherbrooke Ouest
Montreal, Québec
CANADA (H3A 2T7)

Temporary Address

Start Date
End Date

Primary Affilliation Name

McGill University

Start Date 08/2007

Primary Affiliation Address

Pavillion Leacock 418
855 rue Sherbrooke Ouest
Montreal, Québec
CANADA (H3A 2T7)

Contact numbers

Phone

Primary (514) 398-2880 office

Secondary

Temporary

Start Date End Date

Fax

Primary (514) 398-4938

Temporary

Start Date End Date

Electronic Addresses

E-Mail
erin.strumpf@mcgill.ca

Web page address
http://people.mcgill.ca/erin.strumpf/

Citizenship

Canadian [ ] Other [X]

Other Country of Citizenship UNITED STATES

Permanent Residence in Canada

Permanent Resident [X] Date of permanent residency status 22/06/2009 (DD/MM/YYYY)

Have you applied for permanent residency? Yes [ ] No [ ]

Correspondence Language

English [X] French [ ]

Gender

Male [ ] Female [ ]

Date of Birth (DD/MM/YYYY)

Language	Read	Write	Speak	Understand
English (Yes or No)	YES	YES	YES	YES
French (Yes or No)	YES	YES	YES	YES

Other Languages: Spanish

Expertise

List up to ten (10) key words that best describe your expertise in research, instruments and technique.

Health Economics	Vulnerable Populations
Health Policy	Health Insurance
Health Care Financing	Health and Labor Markets
Health Services Research	Minority Health
Population Health	Causal Inference

Indicate and rank the disciplines that best correspond to your research interests. No additional pages may be added.

	Discipline		Sub Discipline	
Rank	**Code**	**Description**	**Code**	**Description**
1.	100	ECONOMICS		
2.	91	HEALTH SCIENCES, APPLIED AND HEALTH SERVICES DELIVERY	1076	Health Services Research - General
3.	91	HEALTH SCIENCES, APPLIED AND HEALTH SERVICES DELIVERY	1109	Population Health - General
4.	91	HEALTH SCIENCES, APPLIED AND HEALTH SERVICES DELIVERY	988	Health Care Delivery
5.	13	CANCER/ONCOLOGY	989	Cancer Prevention
6.				
7.				
8.				
9.				
10.				
11.				
12.				
13.				
14.				
15.				

Academic Background - One additional page may be added

Indicate all university degrees obtained and those in progress (where applicable) starting with the most recent. If you hold a co-degree from more than one institution (e.g. under the Soutien aux cotutelles de these de doctorat agreement between Quebec and France) enter each institution separately. Do not enter honorary degrees here, they should be listed in the Distinctions section.

Also indicate research training, such as postdoctoral or fellowship training. Trainees only: also list undergraduate and graduate research training experience.

Degree Type	Degree Name and Specialty	Institution/Organization and Country	Supervisor name	Start date (MM/YYYY)	Date received or expected (MM/YYYY)
Doctorate (PhD)	Health Policy Economics	Harvard University UNITED STATES	Thomas G. McGuire	09/2002	06/2007
Bachelor's	Economics and Latin American Studies Economics and Latin American Studies	Smith College UNITED STATES	Nola Reinhardt	09/1993	05/1997

Work Experience

Starting with the most recent, indicate your current position, where applicable, and other academic and non-academic position(s) since the beginning of your university studies. For your current positions leave the end date blank. Additional pages will be accepted.

Position	Institution/Organization and Country	Department/Division and Faculty/School	Start Date (MM/YYYY)	End Date (MM/YYYY)
Researcher	CIRANO CANADA		01/2009	
Assistant Professor	McGill University CANADA	Economics Arts	08/2007	
Assistant Professor	McGill University CANADA	Epidemiology and Biostatistics Medicine	08/2007	
Teaching Assistant	Harvard University UNITED STATES		09/2003	06/2005
Research Assistant	National Bureau of Economic Research, Inc. UNITED STATES		06/2003	06/2005
Consultant	Harvard University UNITED STATES		08/2003	02/2005
Special Assistant to the President	The Commonwealth Fund UNITED STATES		06/1999	01/2002

Distinctions / Awards / Credentials

Starting with the most recent, indicate any recognitions received, including awards, fellowships, scholarships, licenses, qualifications, professional designation or credentials. Do not include Academic Appointments here, as they are detailed under Work Experience. Maximum 20 entries.

Name/Title and Type	Institution/Organization and Country	Effective Date (MM/YYYY)	End Date (MM/YYYY)	Specialty	Total Amount
Best New Investigator Poster Research Presentation Distinction	The International Society For Pharmacoeconomics And Outcomes Research UNITED STATES	05/2009			
John A. Heinz Dissertation Award Honorable Mention Distinction	National Academy of Social Insurance UNITED STATES	01/2008			
Dissertation Completion Fellowship Research award	Graduate School of Arts and Sciences, Harvard University UNITED STATES	07/2006	06/2007		$23,000
Pre-Doctoral Fellow in Aging and Health Care Research award	National Bureau of Economic Research UNITED STATES	07/2005	06/2007		$51,000
Merit Award Research award	Graduate School of Arts and Sciences, Harvard University UNITED STATES	07/2005	06/2006		$17,500
Pre-Doctoral Training Grant Research award	U.S. Agency for Healthcare Research and Quality UNITED STATES	09/2002	08/2004		$40,000

Patents and Intellectual Property Rights

Record the total numbers of patents / copyrights in the following table.

OBTAINED			APPLICATIONS UNDER PROCESS			TOTAL PATENTS AND INTELLECTUAL PROPERTY RIGHTS
Total individual	Total collective	Sub-total	Total individual	Total collective	Sub-total	
0	0	0	0	0	0	0

PUBLICATIONS AND PRESENTATIONS

Give the number of publications and presentations in the course of your career. Detailed information should be attached as specified in the "Contributions - details" section.

Publications	Refereed Articles	Books and Monographs	Proceedings / Book Chapters / Contributions to a collective work	Abstracts / Notes	TOTALS
Already Published	2	0	8	0	10
Accepted or in the Press	2	0	0	0	2
					12

Invited presentations	41

LITERARY AND ARTISTIC WORKS

Provide the number of literary and artistic works created in the course of your career. Detailed information should be attached as specified in the "Contributions - details" section.

IN CIRCULATION			IN PROGRESS			TOTAL LITERARY AND ARTISTIC WORKS
Total individual	Total collective	Sub-total	Total individual	Total collective	Sub-total	
0	0	0	0	0	0	0

Supervisory Experience: To be completed by applicants requesting research trainees as part of their budget, salary support candidates and proposed supervisors of trainees.

Indicate the number of graduate students and postdoctoral fellows that you currently supervise or co-supervise. CIHR defines supervisory experience as the formal supervision or co-supervision of trainees. Enter zero (0) if not applicable.

Master 3 Doctoral 1 Post-Doctoral 1

Complete this form by listing the trainees that you have supervised/co-supervised (and are currently supervising/co-supervising) within the last five (5) years. Additional pages may be added if necessary.
* Flag those where you were/are the Primary Supervisor.

*	Name of Student	Program Type	Dates		Degree received or expected	Year Degree Rec'd (YYYY)	Research Project (Short title)	Current position and Institution
			Support Period From (MM/YY	To (MM/YYYY)				
*	Julie Heroux	Graduate Student	09/2010		Master's		Comparison of statistical models for health care utilization and cost data	
	Leah Smith	Graduate Student	09/2010		Doctorate (PhD)		The health and economic impact of Ontario's Grade 8 HPV vaccination program	
*	Roxane Borges Da Silva	Postdoctoral Fellow, PhD	04/2010				Provider practice patterns in Quebec's Family Medicine Groups	
*	Coyle, Natalie	Graduate Student	09/2009		Master's		Primary Health Care Reform: Who Participates in an Integrated Care Model?	
*	Charters, Thomas	Graduate Student	09/2009		Master's		The impacts of organized colorectal cancer screening programs in Canada	
*	Barua, Shourov	Graduate Student	09/2008		Master's	2009	The Impact of Marital Status on Obesity and Overweight in Canada	
*	Musni, Tracy	Graduate Student	09/2008		Master's	2009	Paternal Education and Child Health: Evidence from Indonesia	
	Sirjoosingh, Candace	Graduate Student	09/2008		Master's		Racial Disparities in Cervical Cancer Survival and Treatment in the United States	

Supervisory Experience: To be completed by applicants requesting research trainees as part of their budget, salary support candidates and proposed supervisors of trainees.

Indicate the number of graduate students and postdoctoral fellows that you currently supervise or co-supervise. CIHR defines supervisory experience as the formal supervision or co-supervision of trainees. Enter zero (0) if not applicable.

Master 3 Doctoral 1 Post-Doctoral 1

Complete this form by listing the trainees that you have supervised/co-supervised (and are currently supervising/co-supervising) within the last five (5) years. Additional pages may be added if necessary.
* Flag those where you were/are the Primary Supervisor.

*	Name of Student	Program Type	Dates		Degree received or expected	Year Degree Rec'd (YYYY)	Research Project (Short title)	Current position and Institution
			Support Period From (MM/YY	To (MM/YYYY)				
	Stang, Antonia	Graduate Student	09/2007	08/2009	Master's	2009	Pediatric Emergency Department Wait Times and Process Measures	
	Jenkins, Tania	Graduate Student	09/2007	06/2009	Master's	2009	Arduous Access: Challenges Surrounding Access To Family Doctors In Quebec, Canada	
*	Clement, Olivia	Graduate Student	09/2007	08/2008	Master's	2008	Prices of Anti-Retroviral HIV/AIDS Drugs and Pharmaceutical Company Profits and Research & Development Spending	

Funds REQUESTED

List all sources of support applied for (including CIHR) as an applicant or as a co-applicant. Include the principal applicant's name, title of the proposal, funding source, program name, total amount requested (in Canadian dollars) and the period of the support. Indicate your role in the funding (principal applicant/project leader or co-applicant).

Title of Proposal		
The Effect of Primary Care on Health Care System Outcomes: Health Services Utilization, Health Care Spending, and Population Health		
Funding Source	**Program Name**	
Canadian Institutes of Health Research (CIHR)	New Investigator Salary Award	
Principal Applicant / Project Leader	**Your Role**	
	Principal Applicant	
Total Amount (CAN$)	**Support Period From (MM/YYYY)**	**To (MM/YYYY)**
$300,000	07/2011	06/2016

Title of Proposal		
Examining the Impact of Social Policies on Health Equity: How Policies Designed to Reduce Poverty and Gender Inequality Affect Morbidity and Mortality in Children and Women under 45		
Funding Source	**Program Name**	
Canadian Institutes of Health Research (CIHR)	Programmatic Grant in Health and Health Equity	
Principal Applicant / Project Leader	**Your Role**	
Heymann, Jody	Co-Applicant	
Total Amount (CAN$)	**Support Period From (MM/YYYY)**	**To (MM/YYYY)**
$1,985,051	06/2011	06/2016

Title of Proposal		
The Effect of Primary Care on Health Care System Outcomes: Health Services Utilization, Health Care Spending, and Population Health		
Funding Source	**Program Name**	
Fonds de la Recherche en Santé du Québec (FRSQ)	Chercheurs-boursiers	
Principal Applicant / Project Leader	**Your Role**	
	Principal Applicant	
Total Amount (CAN$)	**Support Period From (MM/YYYY)**	**To (MM/YYYY)**
$240,000	07/2011	06/2015

Title of Proposal		
Methods to measure (and measures of) the (actual) mortality reductions produced by cancer screening		
Funding Source	**Program Name**	
Canadian Institutes of Health Research (CIHR)	Operating Grant	
Principal Applicant / Project Leader	**Your Role**	
Hanley, James	Co-Applicant	
Total Amount (CAN$)	**Support Period From (MM/YYYY)**	**To (MM/YYYY)**
$175,200	10/2011	09/2014

Funds CURRENTLY HELD

List all sources of support currently held (including CIHR) as an applicant or as a co-applicant. Include the principal applicant's name, title of the proposal, funding source, program name, total amount awarded (in Canadian dollars) and the period of the support. Indicate your role in the funding (principal applicant/project leader or co-applicant).

Title of Proposal		
Building capacity for furthering the economic and social case for investment in chronic non-communicable disease prevention and health promotion		
Funding Source	**Program Name**	
Public Health Agency of Canada (PHAC	Request for Standing Offer	
Principal Applicant / Project Leader	**Your Role**	
Dubé, Laurette	Co-Applicant	
Total Amount (CAN$)	**Support Period From (MM/YYYY)**	**To (MM/YYYY)**
$2,000,000	10/2009	09/2016

Title of Proposal		
La prise en charge de la dépression chez les adultes atteints de maladies physiques chroniques		
Funding Source	**Program Name**	
Fonds de la Recherche en Santé du Québec (FRSQ)	SUBVENTIONS DE RECHERCHES EN SANTÉ MENTALE	
Principal Applicant / Project Leader	**Your Role**	
McCusker, Jane	Co-Applicant	
Total Amount (CAN$)	**Support Period From (MM/YYYY)**	**To (MM/YYYY)**
$800,000	07/2009	06/2013

Title of Proposal		
For Whom the Bill Tolls: Private Drug Insurance in Canada		
Funding Source	**Program Name**	
Canadian Institutes of Health Research (CIHR)	Operating Grant	
Principal Applicant / Project Leader	**Your Role**	
Law, Michael	Co-Applicant	
Total Amount (CAN$)	**Support Period From (MM/YYYY)**	**To (MM/YYYY)**
$269,192	10/2010	10/2012

Title of Proposal		
The Effect of Primary Care on Health Care System Outcomes: Health Services Utilization, Health Care Spending, and Population Health		
Funding Source	**Program Name**	
Canadian Institutes of Health Research (CIHR)	Operating Grant	
Principal Applicant / Project Leader	**Your Role**	
	Principal Applicant	
Total Amount (CAN$)	**Support Period From (MM/YYYY)**	**To (MM/YYYY)**
$315,167	01/2009	03/2012

Funds CURRENTLY HELD

List all sources of support currently held (including CIHR) as an applicant or as a co-applicant. Include the principal applicant's name, title of the proposal, funding source, program name, total amount awarded (in Canadian dollars) and the period of the support. Indicate your role in the funding (principal applicant/project leader or co-applicant).

Title of Proposal Examining the Impact of Social Policies on Health Equity: How Policies Designed to Reduce Poverty and Gender Inequality Affect Morbidity and Mortality in Children and Women under 45		
Funding Source Canadian Institutes of Health Research (CIHR)	**Program Name** Programmatic Grant in Health and Health Equity (LOI)	
Principal Applicant / Project Leader Heymann, Jody	**Your Role** Co-Applicant	
Total Amount (CAN$) $14,959	**Support Period From (MM/YYYY)** 12/2010	**To (MM/YYYY)** 06/2011

Title of Proposal Cost-benefit analysis of nursing human resources management policies		
Funding Source Ministère des Finances, de l'Économie et de la Recherche (MFER) (Québec)	**Program Name** Research grants awarded through CIRANO	
Principal Applicant / Project Leader	**Your Role** Principal Applicant	
Total Amount (CAN$) $37,200	**Support Period From (MM/YYYY)** 05/2010	**To (MM/YYYY)** 04/2011

Title of Proposal		
Funding Source	**Program Name**	
Principal Applicant / Project Leader	**Your Role**	
Total Amount (CAN$)	**Support Period From (MM/YYYY)**	**To (MM/YYYY)**

Title of Proposal		
Funding Source	**Program Name**	
Principal Applicant / Project Leader	**Your Role**	
Total Amount (CAN$)	**Support Period From (MM/YYYY)**	**To (MM/YYYY)**

Funds HELD IN THE LAST FIVE YEARS

List all sources of support held in the last five years (including CIHR) as an applicant or as a co-applicant. Include the principal applicant's name, title of the proposal, funding source, program name, total amount awarded (in Canadian dollars) and the period of the support. Indicate your role in the funding (principal applicant/project leader or co-applicant).

Title of Proposal Canadian Health Economics Study Group Annual Meeting		
Funding Source Canadian Institutes of Health Research (CIHR)	**Program Name** Meetings, Planning and Dissemination Grant	
Principal Applicant / Project Leader	**Your Role** Principal Applicant	
Total Amount (CAN$) $7,500	**Support Period From (MM/YYYY)** 02/2010	**To (MM/YYYY)** 01/2011

Title of Proposal Geographic Variation in Medical Services Across Canada: Impacts of Fee-for-Service Payment Schedules		
Funding Source Ministère des Finances, de l'Économie et de la Recherche (MFER) (Québec)	**Program Name** Research grants awarded through CIRANO	
Principal Applicant / Project Leader	**Your Role** Principal Applicant	
Total Amount (CAN$) $60,000	**Support Period From (MM/YYYY)** 01/2009	**To (MM/YYYY)** 01/2010

Title of Proposal		
Funding Source	**Program Name**	
Principal Applicant / Project Leader	**Your Role**	
Total Amount (CAN$)	**Support Period From (MM/YYYY)**	**To (MM/YYYY)**

Title of Proposal		
Funding Source	**Program Name**	
Principal Applicant / Project Leader	**Your Role**	
Total Amount (CAN$)	**Support Period From (MM/YYYY)**	**To (MM/YYYY)**

Strumpf EC, 2011. "Medicaid's Effect on Single Women's Labor Supply: Evidence from the Introduction of Medicaid," *Journal of Health Economics,* in press. This paper examines the extent to which predicted labor supply disincentives associated with the Medicaid program actually occur. A copy of this article was requested by the U.S. Congressional Budget Office to inform analysis of the labor market effects of the 2010 Patient Protection and Affordable Care Act.

Strumpf EC, 2011. "Racial/Ethnic Disparities in Primary Care: The Role of Physician-Patient Concordance," *Medical Care*, in press. This paper addresses whether discrimination and bias can account for disparities in primary health care outcomes. This work has been presented at several conferences and invited seminars.

Strumpf EC, Chai Z, and Kadiyala S, 2010. "Adherence to cancer screening guidelines across Canadian provinces: an observational study," *BMC Cancer*, 10:304. This article presents a novel measure of cancer screening guideline compliance and compares screening patterns and compliance across Canadian provinces for breast, colorectal, and prostate cancer. I presented the research at several national health services research conferences.

Strumpf EC, 2010. "Employer-Sponsored Health Insurance for Early Retirees: Impacts on Retirement, Health, and Health Care," *International Journal of Health Care Finance and Economics*, 10(2); p. 105-147. The study examines the varied impacts of declines in employer-sponsored health insurance for early retirees in the U.S. I have presented this work at several conferences and invited seminars. It has garnered interest among health policymakers, employers and health and labor economists.

Harvard University, Kennedy School of Government, Consultant, 2003-2005: Translated research findings for policymakers writing policy briefs for the Bipartisan Congressional Health Policy Conference attended by members of the U.S. Congress.

- Strumpf EC, "Issues Related to State and Employer Innovations in Insurance Coverage"
- Strumpf EC and Cubanski J, "Options for Federal Coverage of the Uninsured in 2005"
- Strumpf EC, "The Obesity Epidemic in the United States: Causes and Extent, Risks and Solutions"

Academic Honors, Grants and Awards

2010 - 2012 CIHR Operating Grant "For Whom the Bill Tolls: Private Drug Insurance in Canada" Co-investigator (PI Law)
2010 - 2011 Quebec Finance Ministry through CIRANO, "Cost-benefit analysis of nursing human resources management policies" PI (CI J. Castonguay)
2010 - 2011 CIHR Programmatic Grant in Health and Health Equity (LOI), "Examining the Impact of Social Policies on Health Equity: How Policies Designed to Reduce Poverty and Gender Inequality Affect Morbidity and Mortality in Children and Women under 45" Co-investigator (PI Heymann)
2010 CIHR Meetings, Planning and Dissemination Grant "Canadian Health Economics Study Group: Annual Meeting 2010" PI
2009 - 2012 CIHR Operating Grant "The Effect of Primary Care on Health Care System Outcomes: Health Services Utilization, Health Care Spending, and Population Health" PI
2009 - 2013 FRSQ Mental Health Research Grant "Management of Depression Among Adults with Co-Morbid Chronic Illness" Co-investigator (PI McCusker)
2009 - 2016 PHAC Standing Offer "Building capacity for furthering the economic and social case for investment in chronic non-communicable disease prevention and health promotion" (PI Dubé)
2009 Quebec Finance Ministry contract through CIRANO "Geographic Variation in Medical Services Across Canada: Impacts of Fee-for-Service Payment Schedules" PI with Léger
2009 ISPOR Best New Investigator Poster Research Presentation
2008 John A. Heinz Dissertation Award, Honorable Mention, National Academy of Social Insurance
2005 – 2007 Pre-Doctoral Fellow in Aging and Health Care, NBER

External Evaluation Activities

- Reviewer: *The B.E. Journal of Economic Analysis & Policy (1), BMC Public Health (1), CMAJ - Canadian Medical Association Journal (2), Epidemiology (1), Healthcare Policy (1), Inquiry (1), Journal of Health Economics (8), Journal of Human Resources (1), Medical Care (1)*
- Member, CIHR Financing, Sustainability and Governance Working Group, 2011
- Member, CIHR Peer Review Committees
    - Partnerships for Health System Improvement Program, 2009
    - Health Services Evaluation & Interventions Research, 2010 - 2011
- Grant reviewer (external), SSHRC Standard Research Grant Competition, 2009-2010

Supervisory Experience

- Primary supervisor: Master's (3 economics, 2 epidemiology), Undergraduate independent study (4 economics), research assistants (4)
- Co-supervisor: Post-doc (1), Ph.D. (1 epidemiology), Master's (2 epidemiology, 1 biostatistics, 1 sociology), full-time research associate (1)

Presentations (24 before 2009 not included)

2010: American Society of Health Economists, CIHR Primary Healthcare Summit, UBC Center for Health Services and Policy Research
2009: AcademyHealth Annual Research Meeting, Canadian Association for Health Services and Policy Research, Canadian Council on Integrated Healthcare, Canadian Economics Association, Causal Inference in Statistics and the Quantitative Sciences Workshop, International Society for Pharmacoeconomics and Outcomes Research, McMaster University CHEPA Workshop, NBER Summer Institute

Published refereed papers

Economics (authors listed alphabetically)

Strumpf EC, 2011. "Medicaid's Effect on Single Women's Labor Supply: Evidence from the Introduction of Medicaid." *Journal of Health Economics,* in press. (Funding: US National Institute on Aging, grant number T32-AG00186.)

Strumpf EC, 2010. "Employer-Sponsored Health Insurance for Early Retirees: Impacts on Retirement, Health, and Health Care," *International Journal of Health Care Finance and Economics*, 10(2); p. 105-147. (Funding: US National Institute on Aging, grant number T32-AG00186.)

Medicine and Policy (authors listed by contribution)

Strumpf EC, 2011. "Racial/Ethnic Disparities in Primary Care: The Role of Physician-Patient Concordance," *Medical Care*, in press. (Funding: US National Institute on Aging, grant number T32-AG00186, and the US National Institute of Mental Health, grant number M11147-101.)

Strumpf EC, Chai Z, and Kadiyala S, 2010. "Adherence to cancer screening guidelines across Canadian provinces: an observational study," *BMC Cancer*, 10:304. (Role: study conception and design, data acquisition, data analysis and interpretation, draft and revise manuscript; Contribution 70%)

Submitted refereed papers

Medicine and Policy

Hutchison B, Levesque JF, **Strumpf EC**, and Coyle N, "Primary Health Care in Canada: Systems in Motion" (Role: study conception, data acquisition, data interpretation, revise manuscript; Contribution 25%) (Revised and resubmitted at the *Milbank Quarterly*)

Kadiyala S and **Strumpf EC**, "Are U.S. and Canadian Cancer Screening Rates Consistent with Guideline Information Regarding the Age of Screening Initiation?" (Role: study conception and design, data acquisition, data analysis and interpretation, draft and revise manuscript; Contribution 40%) (Revise and resubmit at the *International Journal for Quality in Health Care*)

Presentations as guest speaker

University of British Columbia, Center for Health Services and Policy Research seminar, "Cancer screening policy and the effectiveness of population-based screening: evidence from the U.S. and Canada." October 2010.

McMaster University, Centre for Health Economics and Policy Analysis Workshop on Equity in Health and Health Care, "Racial/Ethnic Disparities in Primary Care: The Role of Physician-Patient Concordance." December 2009.

Canadian Council on Integrated Healthcare, "The Economics of Healthy Living and Patient Responsibility," June 2009.

St. Mary's Hospital, Department of Epidemiology and Community Studies research seminar, "The Effect of Primary Care on Health Care System Outcomes: Developing a New Research Agenda to Evaluate the Impact of GMFs on Utilization, Costs, and Health." May 2009.

Banff International Research Station, Causal Inference in Statistics and the Quantitative Sciences Workshop, "An Applied Economist's Toolkit for Causal Inference." May 2009.

Quebec Research Group on Equity of Access and Organization of Primary Health Care Services (GRÉAS 1), Scientific Conference, "The Effect of Primary Care on Health Care System Outcomes: Developing a New Research Agenda to Evaluate the Impact of GMFs on Utilization, Costs, and Health." December 2008.

Dartmouth College, Rockefeller Center Faculty Workshop in Health Policy, "Racial/Ethnic Disparities in Outpatient Primary Care: The Role of Physician-Patient Concordance." April 2008.

Research reports and reports produced for government

Leger PT and **Strumpf EC**, 2009. "Système de paiement des médecins : bref de politique" (The Physician Payment System: Policy Brief), Quebec Finance Ministry. (Role: study conception and design, revise manuscript; Contribution 20%) (Funding: Quebec Finance Ministry.)

Leger PT and **Strumpf EC**, 2009. "Impact des paiements relatifs sur le taux d'utilisation de procédures médicales: Étude de faisabilité" (The Impact of Relative Payments on the Utilization of Medical Procedures: Feasibility Study), Quebec Finance Ministry. (Role: study conception and design, data acquisition, data analysis and interpretation, draft and revise manuscript; Contribution 80%) (Funding: Quebec Finance Ministry.)

Strumpf EC, 2005. "Issues Related to State and Employer Innovations in Insurance Coverage," The 2005 Commonwealth Fund/John F. Kennedy School of Government Bipartisan Congressional Health Policy Conference, The Commonwealth Fund, July.

Strumpf EC and Cubanski J, 2005. "Options for Federal Coverage of the Uninsured in 2005," The 2005 Commonwealth Fund/John F. Kennedy School of Government Bipartisan Congressional Health Policy Conference, The Commonwealth Fund, July. (Role: study conception and design, data acquisition, data interpretation, draft and revise manuscript; Contribution 70%)

Strumpf EC, 2004. "The Obesity Epidemic in the United States: Causes and Extent, Risks and Solutions," The 2004 Commonwealth Fund/John F. Kennedy School of Government Bipartisan Congressional Health Policy Conference, The Commonwealth Fund, Nov.

Duchon L, Schoen C, Doty M, Davis K, **Strumpf EC** and Bruegman S, 2001. "Security Matters: How Instability in Health Insurance Puts U.S. Workers at Risk - Findings from The Commonwealth Fund 2001 Health Insurance Survey," The Commonwealth Fund, Dec. (Role: data analysis and interpretation, revise manuscript; Contribution 20%)

Collins K, and **Strumpf EC**, 2000. "Living Longer, Staying Well: Promoting Good Health for Older Women," The Commonwealth Fund, Sept. (Role: data analysis and interpretation, draft and revise manuscript; Contribution 65%)

Schoen C, **Strumpf EC**, Davis K, Osborn R, Donelan K, and Blendon R, 2000. "The Elderly's Experiences with Health Care in Five Nations: Findings from the Commonwealth Fund 1999 International Health Policy Survey," The Commonwealth Fund, May. (Role: data analysis and interpretation, draft and revise manuscript; Contribution 70%)

Schoen C, Davis K, DesRoches C, Donelan K, Blendon R, and **Strumpf EC**, 2000. "Equity in Health Care Across Five Nations: Summary Findings from an International Health Policy Survey," The Commonwealth Fund, May. (Role: data analysis, revise manuscript; Contribution 20%)

Schoen C, **Strumpf EC**, and Davis K, 2000. "A Vote of Confidence: Attitudes Toward Employer-Sponsored Health Insurance," The Commonwealth Fund, Jan. (Role: data analysis and interpretation, draft and revise manuscript; Contribution 70%)

Erin Strumpf, Prof.

From: ees.jhe.2.f1e76.4b68e559@eesmail.elsevier.com on behalf of Editorial Office [econ41@york.ac.uk]
Sent: Friday, February 11, 2011 10:44 AM
To: Erin Strumpf, Prof.
Cc: econ41@york.ac.uk; ads6@york.ac.uk
Subject: Your Submission

Ref.: Ms. No. JHE2346R1
Medicaid's Effect on Single Women's Labor Supply: Evidence from the Introduction of Medicaid Journal of Health Economics

Dear Professor Strumpf,

Thank you for revising and resubmitting your paper, which I enjoyed reading. I'm happy that you have met the concerns raised by the referees and I am pleased to tell you that your work has now been accepted for publication in the Journal of Health Economics. Congratulations!

I'd suggest that you italicise the letters referring to the budget constraints on page 9 - coupled with reference to the AFDC there's rather a flurry of letters! And you have a redundant 'since' on line 37 page 14.

Your manuscript will now be forwarded to Elsevier for further processing and all future correspondence will be with the Publishers.

Thank you for submitting your work to this journal and for making such a stimulating and carefully analysed contribution.

With kind regards

Andrew Street
Editor
Journal of Health Economics

****

Erin Strumpf, Prof.

From: em.mdc.0.202b62.69c4a336@editorialmanager.com on behalf of Medical Care [medicalcare@comcast.net]
Sent: Tuesday, January 04, 2011 11:09 AM
To: Erin Strumpf, Prof.
Subject: MDC-D-10-00437R2, MDC Decision

Jan 04, 2011

RE: MDC-D-10-00437R2, entitled "Racial/Ethnic Disparities in Primary Care: The Role of Physician-Patient Concordance"

Dear Dr. Strumpf,

I am pleased to inform you that your work entitled "Racial/Ethnic Disparities in Primary Care: The Role of Physician-Patient Concordance" has now been accepted for publication in Medical Care. All manuscript materials will be forwarded immediately to the production staff for placement in an upcoming issue.

Please follow the instructions for authors. And, make sure to only submit items as Supplemental Digital Contents that will appear only online and not in the print version of Medical Care.

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