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Prevalence of incidental prostate cancer: A systematic review of autopsy studies

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Prostate cancer screening may detect nonprogressive cancers, leading to overdiagnosis and overtreatment. The potential for overdiagnosis can be assessed from the reservoir of prostate cancer in autopsy studies that report incidental prostate cancer rates in men who died of other causes. We aimed to estimate the age-specific incidental cancer prevalence from all published autopsy studies. We identified eligible studies by searches of Medline and Embase, forward and backward citation searches and contacting authors. We screened the titles and abstracts of all articles; checked the full-text articles for eligibility and extracted clinical and pathology data using standardized forms. We extracted mean cancer prevalence, age-specific cancer prevalence and validity measures and then pooled data from all studies using logistic regression models with random effects. The 29 studies included in the review dated from 1948 to 2013. Incidental cancer was detected in all populations, with no obvious time trends in prevalence. Prostate cancer prevalence increased with each decade of age, OR = 1.7 (1.6–1.8), and was higher in studies that used the Gleason score, OR = 2.0 (1.1–3.7). No other factors were significantly predictive. The estimated mean cancer prevalence increased in a nonlinear fashion from 5% (95% CI: 3–8%) at age <30 years to 59% (95% CI: 48–71%) by age >79 years. There was substantial variation between populations in estimated cancer prevalence. There is a substantial reservoir of incidental prostate cancer which increases with age. The high risk of overdiagnosis limits the usefulness of prostate cancer screening.

Prostate cancer is a leading cause of death among men in developed countries,[1,2] and many urge that men should use the prostate-specific antigen (PSA) test to screen for it. Screening is now common in many countries,[3–6] despite authoritative recommendations that the benefits are outweighed by the harms caused through overdiagnosis and consequent overtreatment of disease that would not progress.[7] If the PSA test is positive (whatever the threshold selected), the next step is prostate biopsy, which is performed with multiple biopsy needles and histological examination to determine whether prostate cancer is present, what grade and its extent. Diagnosis and prognostic stratification is a difficult process, requiring subjective judgments that result in considerable variation between pathologists.[8,9] However, many cores are obtained, areas of cancer may be missed, especially if small.

On the other hand, prostate cancers are identifiable in some very young men and at an increasing rate with age, suggesting that this cancer is usually a slowly developing disease with a long preclinical phase. Symptom development and clinical diagnosis mostly occur in older men if at all: many men with prostate cancer die of other causes, long before any symptoms are clinically manifest.

This means biopsy has a high probability of finding prostate cancers that would never have caused clinical disease,[10] causing overdiagnosis,[11,12] and because many are treated to ensure that all cancers are treated, overtreatment. This is a problem because of the high rates of adverse effects of treatment (such as incontinence and impotence). Ideally, screening programs should only focus on the cancers that will progress, not those that will be harmless.

To quantify the potential for overdiagnosis and overtreatment, the reservoir of prostate cancer has to be defined. One method of doing this comes from case series that report incidental prostate cancer rates from autopsies of men who died

Key words: prostatic neoplasms, mass screening, early detection of cancer, autopsy
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What's new?

Before symptoms of prostate cancer manifest clinically, many men die of other causes. Yet, prostate screening, particularly in older men, frequently turns out positive, resulting in overdiagnosis and overtreatment. This meta-analysis of published autopsy studies shows that incidental prostate cancer increases with age and with the use of sensitive screening strategies, especially in older men. Among men whose prostate cancers are designated "favorable-risk,"ô active surveillance and subsequent biopsy can result in reclassification with higher-grade cancer, purely by chance. The potential for the detection of clinically irrelevant, incidental prostate cancer is high, indicating a need for improved screening strategies.

of other causes. However, the limited sample sizes of each series mean the estimates by ages are uncertain. Further, the prevalence may vary by geography and race (because reported incidence and mortality rates are low in Asian populations; intermediate in men of European origin and high among black Africans and African-Americans).[13,14] Accordingly, we aimed to combine all published autopsy series in adult men to obtain an estimate of mean incidental prostate cancer prevalence by age group, and how much this varies between populations.

Methods

Protocol and registration

The review protocol was not registered as there is no systematic review registry for prevalence studies.

Selection

We included autopsy studies of adult men (>age 18 years) who had no history of preexisting prostate cancer and which included a systematic histological examination of the prostate gland. We excluded studies that did not report on age of the men, did not methodically examine the prostate microscopically through step sectioning or were smaller than 100 men. The principal outcomes were age-stratified rates of incidental prostate cancer on histopathology.

Searching

We searched Medline and Embase using the terms listed in Box 1, with no restrictions on year published, type of publication or language. To identify further papers for inclusion in the review, we ran forward citation searches and checked the references of all papers identified by the search for inclusion in the review. We contacted authors to identify further studies. Finally, we repeated our original search to identify any additional papers published during the period of data collection.

Box 1: Search strategy

1 Prostatic Neoplasms/

2 (prostat* adj3 (neoplasm* or neoplasia* or cancer* or carcinoma* or adenocarcinoma* or tumour* or tumor* or malignan* or pre-malignan* or premalignan*)).tw.

3 Autopsy/

4 (autops* or postmortem* or post-mortem* or post mortem*).tw.

5 (#1 or #2) AND (#3 or 4)

Validity assessment

We planned *a priori* subgroup analysis for the following risk of bias study characteristics: consecutive *versus* nonconsecutive case selection, population-based *versus* hospital-based studies and majority of cancers reported high-grade (Gleason score >6; this threshold has important treatment implications). We also planned subgroup analysis of the following pathology validity characteristics: thoroughness of examination (interval between sections), Gleason score used, possible delay in performing autopsy <72 hr, peer review of diagnosis, immunohistochemical stains used to confirm diagnosis and perineural spread noted in any of the cancers (a feature of prostate cancer).

Study selection and data abstraction

Two authors (CD and PG or JD) checked the titles and abstracts of all potentially relevant English articles, and the full text of these was obtained. One author (CD) reviewed titles and abstracts of all non-English articles with the help of researchers expert in the language in question. Two authors (KB and JD or PG) independently checked all the full-text articles for eligibility. Disagreements were resolved through discussion with a third author (CD).

Two authors independently extracted clinical data (KB and CD) and pathology data (GW and KB) using standardized forms. Disagreements were decided by a third author (PG or CD). We extracted data on mean cancer prevalence, decade-specific cancer prevalence and the validity measures as described above. When data were not available elsewhere in the paper, we extracted data from figures using Plot digitizer software (http://plotdigitizer.sourceforge.net, accessed August 18, 2014).

Quantitative data synthesis

Our main summary measure was the prevalence of previously undiagnosed prostate cancer. We pooled data from all studies using logistic regression models with random intercepts to represent the distribution of underlying cancer prevalences between different populations. This type of model also allowed for the nested structure of the data, with decade-specific prevalence estimates nested within each study. We used the model to examine the impact of the validity characteristics on the estimates of age-adjusted prevalence. SAS 9.3 was used for all analyses. The NLMIXED procedure was used to build the models, as has been recommended.[15]

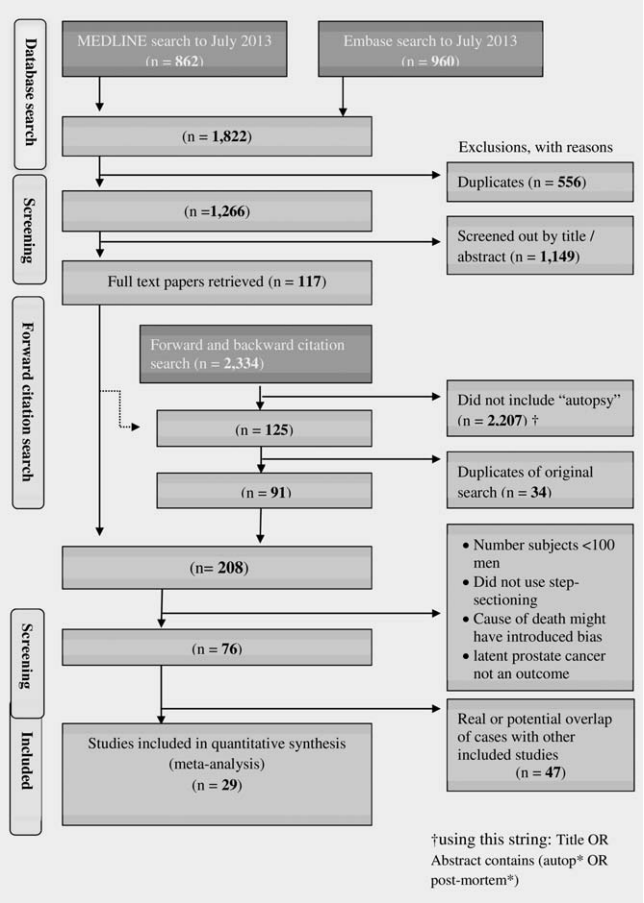

Figure 1. Search and selection of primary studies for the meta-analysis.

Results

The selection of studies is summarized in Figure 1: 1,822 abstracts were identified by Medline and Embase searches and 117 papers were retrieved for full-text review. A further 2,334 papers were identified from the references of these papers, and from forward citation searches of them 91 were retrieved, giving a total of 208 papers that had full-text review. We assessed 129 of these as not meeting our selection criteria. Several of the remaining 76 studies used overlapping data. We contacted authors to resolve some potential overlaps, but, when uncertainty remained, we were conservative, excluding 47 studies that might potentially overlap with others, to avoid the risk of double counting cases. For each set of potentially overlapping reports, we chose the one that reported on the largest number of men, in the most detail (this was usually the most recent report). This left 29 studies[16–44] to be included in the systematic review (Table 1).

Figure 2 shows the overall prevalence of incidental prostate cancer for the studies by year of publication, with size of data points proportional to the number of men in the study. There was no visible trend in estimated prevalence over time from the earliest study, published in 1948 to the most recent study, published in 2013 (we formally test for temporal trend in the age-adjusted model below). Studies performed in earlier Japanese populations gave lower prevalence but more recent studies were not different from those in European-origin populations (there was one outlier Asian study performed on Chinese). There were insufficient data to compare the cancer prevalence in men of African descent to that of other ethnicities.

Data in 25 studies allowed age-specific prevalence calculations thus allowing estimates of changes in cancer prevalence with age (summarized in Fig. 3 and the Supporting Information Appendix Figure). Four studies[33,36,42,44] were excluded as prevalence per decade of age could not be calculated.

Data from 22 studies on the number of men and the number of cases per decade of age available were included in the model analysis. Three studies[18,19,30] in Figure 3 only reported cancer prevalence per decade so could not be included in the model without specific number of cancers and number of men per decade of age. One study had data for all the seven age groups, a further five studies, nine studies, six studies and one study had data for six, five, four and three age groups, respectively. In total, 109 observations were used in the baseline model. There was very strong evidence that cancer prevalence differed between studies (test for random intercepts, $p < 0.001$). Prostate cancer prevalence increased with each decade of age ($p < 0.001$) and this increase was similar for all studies (test for random decade slope, $p = 1.0$). We tested other available validity characteristics in the random intercepts model (adjusted for decade of age, Table 2). We found no evidence that population *versus* hospital based; section thickness; peer review; reporting of perineural spread or possible autolysis affected cancer prevalence, after allowing for the increase in prevalence with age. We also found no statistical evidence that use of immunohistochemical stain or having the majority of cancers with a Gleason score >6 had effects on cancer prevalence, although the confidence intervals for these were both wide reflecting the fact that only four studies used immunohistochemical stains and only one study had majority of cancers with a Gleason score >6. However, there was evidence that studies using the Gleason score reported higher prevalence than those that did not (OR: 2.03) so this was included in the final model. Finally, we found no evidence for a temporal trend in age-adjusted prevalence among the studies overall ($p = 0.11$) or among those published before 1985 ($p = 0.13$) or after this date ($p = 0.75$).

We used the baseline model to estimate the unadjusted mean age-specific prevalence for the different populations (Fig. 3, dashed line). The estimated mean prevalence at age <30 years was 4%; this increased to 49% by age >79 years. The final model adjusted the estimates of studies that did not use Gleason score upwards (Fig. 3, solid line). The estimated mean cancer prevalence at age<30 years was 5% (95% CI: 3–8%); this increased similarly in a nonlinear fashion to 59% (95% CI: 48–71%) by age >79 years. There was substantial variation between populations in estimated cancer prevalence;

Table 1. Characteristics of the 29 included studies

Author	Year published	Country/Ethnicity	Number of men in study	Age (years)	Study population	Mean pathology section width (mm)	Delay before autopsy	Peer review	IHC stain used	Reported perineural spread	GS used	Majority of cancers GS > 6
Breslow[16]	1977	Israel, Hong Kong, Uganda, Jamaica, Sweden, Germany, Singapore	1,327	Mean = 65	Hospital	5	Not noted	Yes	No	No	No	–
Powell[17]	2010[1]	USA	1,056	Range = 20–79	Forensic	2.5	Not noted	No	No	No	Yes	No
Yatani[18]	1988	Japan	660	Mean = 68.7	Hospital	3	Not noted	No	No	No	No	–
Kong[19]	1997	China	506	Range = 15–>70	Forensic	5	Not noted	Yes	Yes	No	Yes	No
Guileyardo[20]	1980	USA: Black and White	500		Both	3	Not noted	Yes	No	No	Yes	–
Yatani[21]	1974	Japan	479		Hospital	5	Not noted	No	No	No	No	–
Liavag[22]	1968	Norway	340	≥40	Hospital	4	<24 hr	No	No	No	No	–
Zlotta[23]	2013	Japanese and Russian	320	Mean = 64.4, range = 22–89	Hospital	4	<24 hr	Yes	No	No	Yes	Yes
Lundberg[24]	1970	Sweden	292		Hospital	5	Not noted	No	No	No	No	–
Oota[25]	1961	Japan	259	≥45	Both	2.5	Not noted	No	No	Yes	No	–
Karube[26]	1961	Japan	229	≥40	Hospital	4.5	Not noted	No	No	No	No	–
Holund[27]	1980	Denmark	216		Hospital	3	Not noted	No	No	Yes	Yes	–
Stamatiou[28]	2006	Greece	212	Range = 30–98	Hospital	4	Not noted	No	No	No	Yes	No
Franks[29]	1954	UK	211		Forensic	4	Not noted	No	No	No	No	–
Ota[30]	1958	Japan	203		Hospital	3	Not noted	No	No	No	No	–
Edwards[31]	1953	Canada	173	Mean = 64.1	Forensic	4	Not noted	Yes	No	Yes	No	–
Harbitz[32]	1973	Norway	172	>40	Hospital	5	Not noted	No	No	No	No	–
Haas[33]	2007	USA	164		Hospital	4		No	Yes	No	Yes	No

Table 1. Characteristics of the 29 included studies (Continued)

Author	Year published	Country/Ethnicity	Number of men in study	Age (years)	Study population	Mean pathology section width (mm)	Delay before autopsy	Peer review	IHC stain used	Reported perineural spread	GS used	Majority of cancers GS > 6
				Median = 64, interquartile range = 54–73			Not noted					
Akazaki[34]	1973	USA: Japanese	158	≥50	Hospital	3	Not noted	No	No	Yes	No	–
Sakr[35]	1993[1]	USA	152	10–50	Forensic	3.5	<24 hr	No	No	No	Yes	No
Billis[36]	2002	Brazil: White, Black, Mullato (+1 Japanese)	150	>40	Hospital	4	Not noted	No	No	No	Yes	No
Zare-Mirzaie[37]	2012	Iran	149	Mean = 64.5, range = 50–91	Forensic	4	Not noted	No	No	No	Yes	No
Sanchez-Chapado[38]	2003	Spain	146	Mean = 48.5, range = 20–80	Forensic	3.5	24 hr	Yes	No	No	Yes	No
Andrews[40]	1949	UK	142	15–79	Hospital	4	54 hr	No	No	Yes	No	–
Soos[39]	2005	Hungary	142	18–92	Hospital	4	36 hr	Yes	Yes	No	Yes	No
Polat[41]	2009	Turkey	114	Mean = 55, range = 25–85	Forensic	4	Not noted	No	No	No	No	
Brawn[42]	1996	USA: Black and White	104	Mean = 69, range = 38–96	Hospital	3	Not noted	No	No	No	No	
Meyenburg[44]	1948	Swiss	100	>40	Hospital	2.5	Not noted	No	No	Yes	No	–
Viitanen[43]	1958	Finland	100	≥50	Hospital	5	Not noted	No	No	No	No	–

[1]Powell and Sakr papers both report data from the Wayne County Autopsy study: Powell reports data on men autopsied from 1992 to 2001; Sakr (accepted for publication Jan 1993) does not specify the time period reported on and there is a possible overlap with Powell for autopsies done in the earlier part of 1992.
Abbreviations: IHC: immunohistochemistry stain; GS: Gleason score.

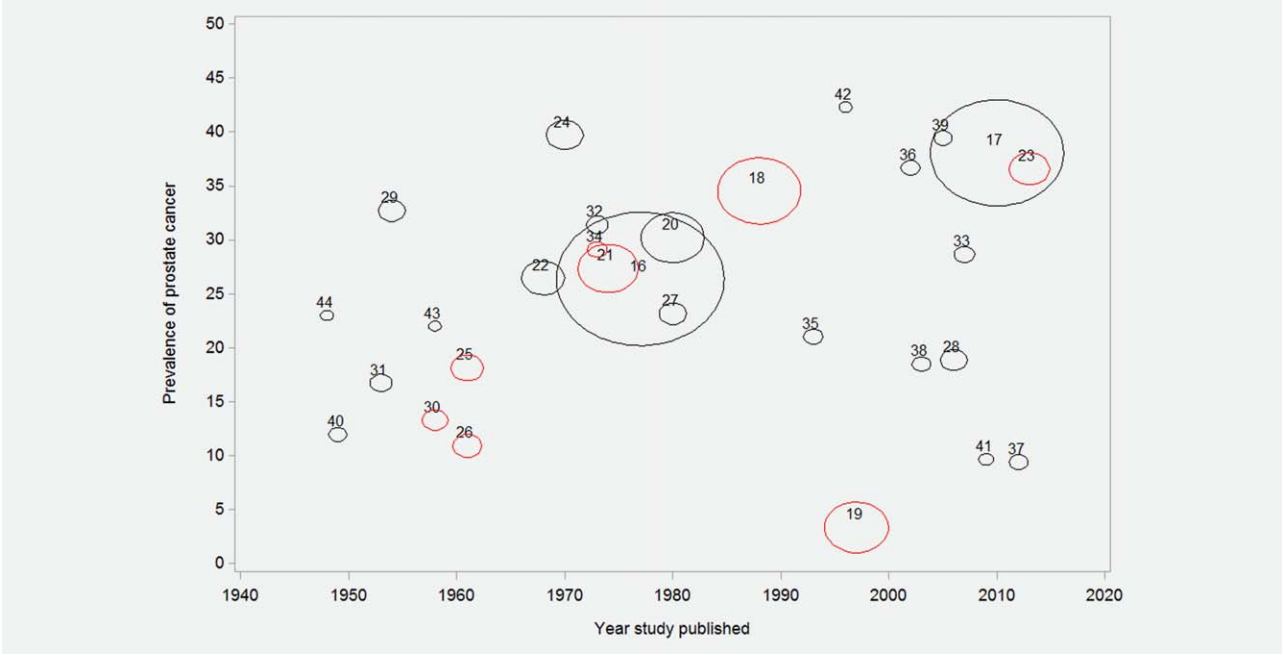

Figure 2. Prevalence of incidental prostate cancer in studies by year of publication.

for example, the 5th, 50th and 95th percentile of cancer prevalence for age <30 years were 2, 5 and 17%, respectively. At age 40–50 years they were 5, 15 and 37%, and at age >79 years 30, 59 and 84%, respectively.

Discussion

We identified 29 studies in more than 20 countries spanning over six decades, which consistently demonstrated a high prevalence of prostate cancer as an incidental finding at autopsy. As expected, the prevalence is most strongly related to age, with the prevalence doubling about every 14 years. Age only explains part of the considerable variation between studies: we could identify only one other clear factor: use of a Gleason score. The studies not using the Gleason grading systems for tumors (dominated by older studies, in western countries) appear to have used conservative criteria for tumor diagnosis, which might explain the lower prevalences. The several other potential factors that might have been predictive (population selection, prostate sampling method and staining technique) were not significant in our model. This may be partly a consequence of incomplete descriptions of methods and the limited statistical power to detect an effect (*e.g.*, few studies used immunohistochemical stains). There may be real differences in cancer prevalence between different populations not accounted for by

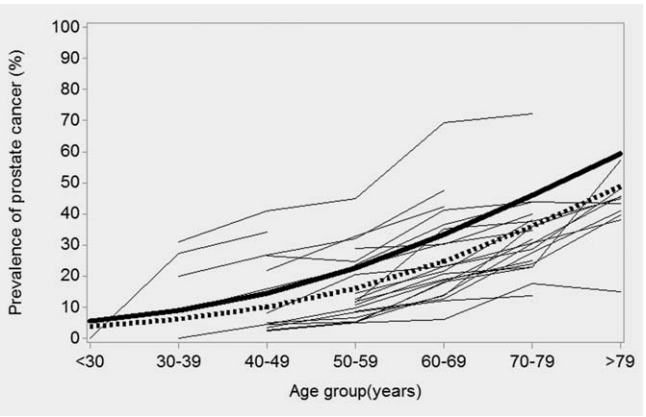

Figure 3. Decade-specific prevalence of: (i) incidental prostate cancer from studies and (ii) mean prevalence from models before and after adjustment for use of Gleason score 294 × 188 mm (100 × 100 DPI).

Table 2. Estimates of odds ratio (from logistic regression model) for 11 possible predictive factors including decade of age

Variable	Odds ratio (95% CI)	*p* Values
Increase in age (per decade)	1.71 (1.62–1.81)	<0.001
IHC stain used	3.38 (0.75–15.31)	0.11
Population *vs.* hospital based	0.78 (0.40–1.53)	0.48
Consecutive cases noted	1.51 (0.78–2.90)	0.21
Section thickness (per mm increase)	0.75 (0.50–1.12)	0.15
Peer review	1.51 (0.73–3.11)	0.25
Perineural spread noted	0.49 (0.26–1.17)	0.11
Gleason score used	2.03 (1.12–3.70)	0.02
Majority had GS > 6	1.07 (0.07–15.74)	0.75
Autolysis unlikely	1.80 (0.89–3.66)	0.09
Time trend (decade paper published)	1.12 (0.96–1.28)	0.11

differences in the way the studies were done. For example, the prevalence of incidental tumors was relatively low in earlier studies of Japanese men, although more recent study estimates are similar to the rest of the world. Other genetic and cultural differences between populations may result in variation in cancer prevalence, but could not be demonstrated in this review.

Our comprehensive search with no language restrictions yielded a considerable number of studies over several decades. The age-adjusted rates of incidental cancer appear to have remained fairly constant over time. This contrasts with the rates of cancer detected during men's lifetimes in many developed countries where the age-adjusted incidence rates dramatically increased after widespread PSA testing, after a slower increase which coincided with increasing use of transurethral resection of the prostate.[45] Whether there has been any increase in the cancers which would progress if untreated remains uncertain; our data suggest that the reservoir of cancers that do not progress has remained more or less the same.

Our study has several limitations, principally the unknown validity of pathological assessment at autopsy. Autolysis has the potential to mimic cancer and might falsely elevate estimates of cancer prevalence. We attempted to test for this by separately analyzing studies with strict inclusion criteria based on minimal delay between death and autopsy, which actually yielded higher cancer prevalences than the remainder. The studies that used pathology practices similar to those currently used in the evaluation of surgical prostate specimens (such as Gleason score, immunohistochemical stain and peer review) also had higher estimates of cancer prevalence than those that did not. Although there was a high proportion of Gleason score $\leq$6 in earlier U.S. series, there is evidence to suggest a "grade creep" over time such that many of these cancers would now be graded as Gleason score >6.[45] The one study with majority Gleason score >6 had similar prevalence estimates to those with majority $\leq$6. Taken together, these findings suggest that our estimates are a true indication of the incidental cancer reservoir rather than mere artifact. Further, if a biopsy of these cancers had been done ante-mortem and assessed using current pathology practices, it appears likely that many would have been classified as high grade and active treatment recommended.

Another limitation was missing details of methods and prevalence of cancer stratified by age and other factors; as many studies were old, contact with authors for clarifications was not possible. Insufficient data meant we were unable to test for differences in prevalence by geography and race. In particular, our sensitive search strategy failed to identify any studies solely in men of African descent that met our inclusion criteria. Fewer than half of the studies were published after 1986 when PSA testing began, and most were in countries where screening was uncommon. In populations where screening has become common this may have lead to underestimation of incidental cancer prevalence among autopsy series that exclude diagnosed men, although the effects are unlikely to be large.[23] Cancers that present clinically will also add to total cancer prevalence in the population, but these are much less common than incidental cancers (A man in the United States has ~10% lifetime risk of symptomatic disease and 3% chance of dying from prostate cancer).[46] Clinical cancers are not the focus of this paper which seeks to estimate the full potential for overdiagnosis when screening for (clinically silent) incidental prostate cancer.

Our findings are in keeping with those of a previous report that included eight autopsy studies[46] and a very recent review that included 56 studies, 24 of which used step sectioning.[14] Some of the studies included in these reviews were excluded from our final selection because there were <100 men or another reason as outlined in Figure 1. Despite differences in the methods used for our review and each of these, the estimated mean age-specific prevalences are broadly similar. The recent review examined age-specific prevalence according to race and found differences between men of Asian (lowest prevalence), European (middle) and African descent (highest prevalence); it was not reported if these were statistically significant.[14] The method used to arrive at these estimates may have been flawed; although race was defined on subsets of men within the studies, the estimates of age-specific prevalence according to race were arrived at by comparison between studies. Differences in the way the studies were conducted, such as the method of pathological examination, may have confounded the apparent effects of race on cancer prevalence. Indeed, the age-specific rates for different races within the individual studies appear much more similar.

Our review, which uses data only from large high-quality primary studies, corroborates the overall age-specific prevalence estimates of the other reviews. Importantly, we also show that although there is substantial variation between study populations, much of this may be due to methodological differences. The more carefully we look for prostate cancer, the more likely we are to find it: evaluating using the Gleason score grading system more than doubled the odds of finding cancer; and although not statistically significant, we estimated that use of a specific immunohistochemical stain to aid diagnosis raised the odds by over three times. Taken together, these data suggest that our findings are conservative estimates and the true incidental cancer prevalence rates may be even higher. This reinforces the maxim that "any excuse to biopsy the prostate has an excellent, age-dependent chance of being positive.[10]" This is now more true than ever, as recent pathology practices (such as those we examined) increase the probability of making a diagnosis of cancer.

The age-specific prevalences demonstrate that screening will cause overdetection. Other methods for estimating the incidence of overdetection have been reported. In the large European Trial of PSA screening men aged 55–69 years (ERSPC), after 13 years follow-up 8% of the screened group had prostate cancer detected (compared to 6% of the controls).[47] Our estimates for men aged 60–70 and aged 70–80 are 33 and 46%, respectively, much higher even than for men

undergoing regular screening. This may reflect the modest sensitivity of PSA to detect cancers, and particularly the probability of even multiple needle biopsies missing a small focus. It suggests that a residual pool of undetected "cancers" is likely, even in intensively screened populations, though the proportion of these that would progress and invade is likely to be much smaller.

There are several clinical implications of these autopsy studies. First is the obvious risk of overdetection during prostate cancer screening. A more sensitive test than PSA, or a lower threshold, and more intense biopsy sampling will increase overdetection. Second, the rate of overdetection will increase with age. Third, the high rates from the study where the majority of incidental cancers were Gleason score >6[23] suggests that men with "favorable-risk cancer" who enter active surveillance have a substantial probability of higher grade cancer being found at a subsequent biopsy, purely due to chance sampling.

Despite these high prevalences of histological findings, few prostate cancers present within men's lifetime if not discovered by screening, and even in intensely screened populations most are left undiscovered. Hence, a key research implication is the urgency of finding better methods of distinguishing progressive from indolent prostate cancers.[48] Future autopsy studies should address validity characteristics identified in this review so that estimates are unbiased and reflect the full extent of the latent cancer reservoir for each age group in the population. They should seek to explain real differences in the frequency of latent cancer by examining and reporting other predictors such as race, geography and family history. Studies are needed in diverse settings, including African and other understudied populations, so that country-specific data may inform local policy decisions on the potential for overdiagnosis with screening.

In conclusion, we found a universal reservoir of latent prostate cancer that increases with age. Proponents of prostate cancer screening need to be wary of the high risk of overdiagnosis.

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Author Contributions

K.J.L.B. contributed to the concept and design, data collection, did the analysis, contributed to the interpretation of data, was responsible for drafting and revising the manuscript and is guarantor for the study. C.D.M. and P.G. conceived the idea for the study, contributed to the design, data collection, interpretation of data and revising the manuscript. G.W. and J.D. contributed to data collection, interpretation of data and revising the manuscript.

Competing Interests

All authors have completed the ICMJE uniform disclosure form at http://www.icmje.org/coi_disclosure.pdf and declare: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years and no other relationships or activities that could appear to have influenced the submitted work.

Transparency Declaration

Katy Bell affirms that the manuscript is an honest, accurate and transparent account of the study being reported; no important aspects of the study have been omitted and any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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