

Screening for Testicular Cancer: An Evidence Review for the U.S. Preventive Services Task Force

Kenneth Lin, MD, and Ruta Sharangpani, MD, MPH

Background: Testicular cancer is the most common type of cancer in men aged 15 to 34 years. Because treatment produces favorable outcomes even in advanced stages, the U.S. Preventive Services Task Force (USPSTF) concluded in 2004 that screening asymptomatic men for testicular cancer is unlikely to produce additional benefits over clinical detection.

Purpose: To search for new evidence on the benefits and harms of screening for testicular cancer to assist the USPSTF in updating its 2004 recommendation.

Data Sources: English-language articles indexed in PubMed and the Cochrane Library and published between 1 January 2001 and 11 November 2009.

Study Selection: Randomized, controlled trials; meta-analyses; systematic reviews; cohort studies; and case-control studies were selected to determine the benefits of screening for testicular cancer. Randomized, controlled trials; meta-analyses; systematic reviews; cohort studies; case-control studies; and case series of large, multisite databases were selected to determine the harms of screening. Each author independently reviewed titles, abstracts, and full-text articles for possible inclusion.

Data Extraction: One author abstracted information on the benefits and harms of screening for testicular cancer.

Data Synthesis: No studies met the inclusion criteria. Three studies were considered for inclusion at the full-text stage of review. These inconclusive studies addressed testicular microlithiasis, *XIST* gene testing, and testis-sparing surgery.

Limitation: The focused search strategy may have missed some smaller studies or studies published in languages other than English on the benefits or harms of testicular cancer screening.

Conclusion: No new evidence was found on the benefits or harms of screening for testicular cancer that would affect the USPSTF's previous recommendation against screening.

Primary Funding Source: Agency for Healthcare Research and Quality.

Ann Intern Med. 2010;153:396-399.

For author affiliations, see end of text.

www.annals.org

Editor's Note: As part of the U.S. Preventive Services Task Force's (USPSTF) ongoing commitment to clarity about its work and methods, it has begun to invite public comment on all draft recommendation statements before publication of the final statements. Because of this new initiative, the recommendation on screening for testicular cancer does not appear with this accompanying background review. The USPSTF's draft recommendation statement on screening for testicular cancer is now available for public comment at www.uspreventiveservicestaskforce.org/tfcomment.htm. Comments will be accepted. The USPSTF will consider submitted comments when it finalizes the recommendation for subsequent publication in *Annals* and posting on the USPSTF Web site at www.uspreventiveservicestaskforce.org.

In 2008, approximately 8000 men in the United States received a diagnosis of testicular cancer, and 380 men died of it. The overall incidence of testicular cancer is 5.4 cases per 100 000 men, and white men have the highest incidence, at 6.3 cases per 100 000 men. The

incidence of testicular cancer has been gradually increasing since 1975 (1). Most testicular tumors are of germ-cell origin, classified as either seminomas or nonseminomas. The peak incidence of testicular cancer occurs between the ages of 15 and 34 years (2). Cryptorchidism and family history are established risk factors for testicular cancer. Researchers are also investigating a possible association between male-factor infertility and testicular cancer (3).

In 2004, the U.S. Preventive Services Task Force (USPSTF) recommended against screening for testicular cancer because of its relative rarity, the lack of evidence showing the accuracy of clinical or self-examination, and highly favorable outcomes from treatment. Instead, the USPSTF encouraged clinicians to consider testicular cancer in their differential diagnosis for patients with testicular symptoms (4). In 2009, the USPSTF decided to update the evidence to reaffirm its previous recommendation. The goal of this reaffirmation update was to search for new, high-quality studies with the potential to change the previous recommendation.

The USPSTF requested that this update address 2 primary key questions:

Key question 1: What are the benefits of screening asymptomatic men for testicular cancer?

Key question 2: What are the harms of screening asymptomatic men for testicular cancer?

See also:

Web-Only

CME quiz

Conversion of graphics into slides

METHODS

Data Sources and Searches

We searched the English-language literature for studies on the benefits and harms of testicular cancer screening in asymptomatic men that were published between 1 January 2001 (the last year searched by the previous USPSTF review) and 11 November 2009, using the search terms *testicular neoplasm with germinoma* and *mass screening or screening*. The initial search was restricted to articles indexed in the Cochrane Database of Systematic Reviews and the PubMed core clinical journal subset (previously known as the Abridged Index Medicus). When the initial search yielded few articles, searches were expanded to include noncore journals. We supplemented these searches by reviewing reference lists of recent reviews and clinical guidelines.

Study Selection

To determine the benefits of screening, we included randomized, controlled trials; meta-analyses; systematic reviews; cohort studies; and case-control studies. To determine the harms of screening, we included randomized, controlled trials; meta-analyses; systematic reviews; cohort studies; case-control studies; and case series of large, multisite databases. We excluded case reports, narrative reviews, editorials, and practice guidelines.

We evaluated articles at the title, abstract, and full-text stage by using predetermined exclusion criteria. Articles selected for further examination by at least 1 author advanced to the next stage of review. At the full-text article stage, differences of opinion were resolved by consensus.

Data Extraction

One author abstracted information on study design, sample size, entry criteria, and other outcomes of interest.

Data Synthesis and Analysis

Data were described and synthesized in a narrative format.

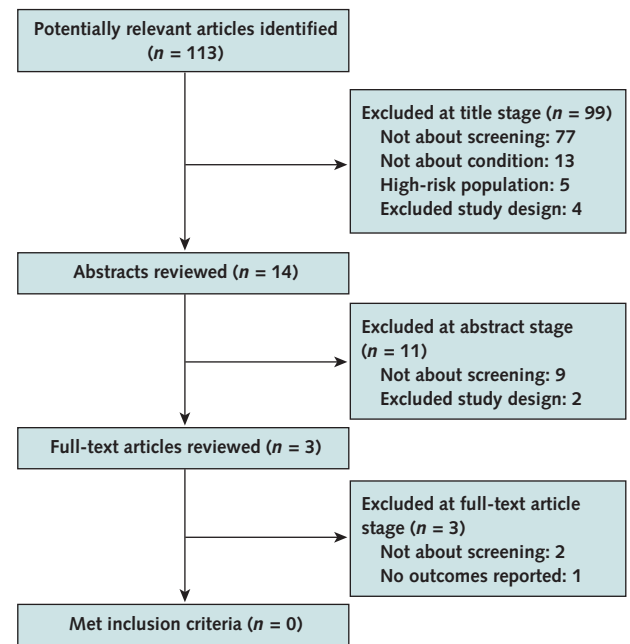
Role of the Funding Source

The work of the USPSTF is supported by the Agency for Healthcare Research and Quality. This review did not receive separate funding.

RESULTS

A total of 113 articles were retrieved and entered into a reference EndNote (Thomson Reuters, New York, New York) database. After sequential review of the titles, abstracts, and full text (**Figure**), we determined that none of the articles met all of the inclusion criteria. The most common reason for exclusion was that the testing or interventions were performed in symptomatic populations. Therefore, we will discuss the 3 articles that reached the full-text review stage (**Table**).

Figure. Study flow diagram.



Key Question 1: What Are the Benefits of Screening Asymptomatic Men for Testicular Cancer?

In 2004, the USPSTF identified no studies showing benefits of screening for testicular cancer. We also found no new studies that directly examined benefits of screening.

Bennett and colleagues (5) prospectively examined the association between testicular microlithiasis and testicular cancer in a cohort of men who had had ultrasonography for testicular problems or for other diagnostic purposes (for example, pain, swelling, or infertility evaluation). Of the 104 men with testicular microlithiasis, 72 had follow-up ultrasonography, with a mean follow-up of 45 months (range, 12 to 90 months). None of the men was found to have testicular tumors. The small sample size of this study, which included only symptomatic patients, makes it difficult to draw any conclusions about the short-term benefit of screening asymptomatic persons.

Kawakami and associates (6) studied the *XIST* gene, which deactivates the X chromosome and thus is normally methylated in men. Previous research has shown that some germ-cell tumors in men have abnormally unmethylated *XIST* genes. This study compared the methylation pattern of the *XIST* gene in patients with and without germ-cell tumors. Plasma samples from 25 patients with testicular cancer were compared with samples from 24 patients with other types of urogenital cancer and from 6 healthy patients. Of the 25 patients with testicular cancer, 16 had unmethylated *XIST* genes; none of the patients in the comparison populations did. Although the study suggests that the *XIST* gene may have promise as a marker for testicular

Table. Excluded Studies With Relevance to Benefits or Harms of Screening for Testicular Cancer

Author, Year (Reference)	Study Design	Sample Characteristics	Intervention or Comparison	Main Results	Additional Information	Summary
Bennett et al, 2001 (5)	Prospective cohort	104 men with testicular microlithiasis	Follow-up ultrasonography	No new testicular tumors detected after a mean follow-up of 45 mo (range, 12 to 90 mo)	All patients had some urologic symptom (e.g., pain, swelling, infertility evaluation) at the time of the initial ultrasonography	Testicular microlithiasis in symptomatic men was not associated with subsequent development of testicular cancer
Kawakami et al, 2004 (6)	Diagnostic accuracy	25 men with testicular germ-cell tumors, 24 men with other types of urogenital cancer, and 6 healthy patients	Detection of unmethylated (abnormal) <i>XIST</i> DNA with specifically designed polymerase chain reaction primer	Unmethylated <i>XIST</i> DNA was found in 16 of 25 plasma samples in men with testicular germ-cell tumors; none of the plasma samples in the comparison groups contained unmethylated <i>XIST</i> DNA	Study was not designed to establish the utility of <i>XIST</i> detection as a screening test in asymptomatic men	Unmethylated <i>XIST</i> DNA may be a genetic marker for testicular cancer
Carmignani et al, 2003 (7)	Retrospective cohort	1320 patients in 1 hospital-based urology clinic, 27 of whom had a testicular tumor identified by ultrasonography	Orchiectomy (12 men) vs. testis-sparing surgery (15 men)	No recurrent tumors in either group after a mean follow-up of 9 mo (range, 1 to 19 mo)	Assignment to type of surgery was not randomized	No difference in short-term tumor recurrence between men who had testis-sparing surgery vs. orchiectomy

cancer, the study’s small sample size and lack of clinical outcomes make drawing conclusions impossible. To establish the utility of the *XIST* gene in a screening test, one would first need to establish the prevalence of the methylated and unmethylated forms in a population of asymptomatic men and follow the 2 groups longitudinally to compare their risk for a diagnosis of testicular cancer.

Key Question 2: What Are the Harms of Screening Asymptomatic Men for Testicular Cancer?

Previous reviews found no studies showing harms from testicular cancer screening, which may include the psychological effects of false-positive results and the cost and complications of unnecessary confirmatory testing. Our review did not find any new studies on the harms of screening for testicular cancer in asymptomatic men.

A study by Carmignani and coworkers (7) compared testis-sparing surgery of testicular tumors with standard orchiectomy. Patients with scrotal or testicular symptoms (for example, swelling, pain, infertility, varicocele, or erectile dysfunction) were eligible for the study. Of the 1320 patients who had had ultrasonography, 27 had tumors; 17 of these tumors were palpable. Of the 27 patients with tumors, 12 had orchiectomy and 15 had testis-sparing surgery. One patient in the conservative surgery group developed a scrotal hematoma. No one in either group showed evidence of recurrent cancer after an average follow-up of 9 months (range, 1 to 19 months). Although the study was not randomized, the authors concluded that conservative surgery did not seem to pose a greater risk for recurrence of testicular cancer.

DISCUSSION

Although we did not identify any studies that directly discussed either the benefits or harms of testicular cancer screening, Carmignani and colleagues (7) needed to perform ultrasonography on 1320 symptomatic men to find 27 tumors. Because symptomatic men have a higher pretest probability of cancer than asymptomatic men, one would expect the number needed to screen to detect 1 case of testicular cancer to be considerably greater, and the false-positive rate substantially higher, than those in the study by Carmignani and colleagues.

There are some established risk factors for testicular cancer, such as cryptorchidism and family history of testicular cancer, but researchers continue to look for new ones. A prospective study of 1504 healthy volunteers (8) found that 84, or approximately 5%, had testicular microlithiasis. After 5 years of follow-up, only 1 participant received a diagnosis of a testicular germ-cell tumor after discovering a palpable mass on self-examination (9).

Although these studies do not directly address the benefits of screening, they serve as a reminder for primary care clinicians to consider testicular cancer as part of their differential diagnosis in patients with testicular or scrotal symptoms. As the USPSTF stated in a previous recommendation statement (10), although the average primary care physician may see only 1 patient with testicular cancer over 20 to 25 years, 26% to 56% of patients with testicular cancer had an initially incorrect diagnosis of another testicular disorder.

In summary, we found no new studies since the 2004 USPSTF recommendation on the benefits or harms of

screening for testicular cancer by testicular self-examination, physician examination, or other screening tests.

From the Agency for Healthcare Research and Quality, Rockville, Maryland.

Potential Conflicts of Interest: None disclosed. Forms can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M09-2048.

Requests for Single Reprints: Kenneth Lin, MD, Center for Primary Care, Prevention, and Clinical Partnerships, Agency for Healthcare Research and Quality, 540 Gaither Road, RM 6107, Rockville, MD 20850; e-mail, Kenneth.Lin@ahrq.hhs.gov.

Current author addresses and author contributions are available at www.annals.org.

References

1. Altekruse SF, Kosary CL, Krapcho M, Neyman N, Aminou R, Waldron W, et al. SEER Cancer Statistics Review, 1975–2007. Bethesda, MD: National Cancer Institute; 2010. Accessed at <http://seer.cancer.gov/statfacts/html/testis.html> on 4 August 2010.

2. McGlynn KA, Devesa SS, Sigurdson AJ, Brown LM, Tsao L, Tarone RE. Trends in the incidence of testicular germ cell tumors in the United States. *Cancer*. 2003;97:63–70. [PMID: 12491506]

3. Walsh TJ, Croughan MS, Schembri M, Chan JM, Turek PJ. Increased risk of testicular germ cell cancer among infertile men. *Arch Intern Med*. 2009;169:351–6. [PMID: 19237718]

4. U.S. Preventive Services Task Force. Screening for Testicular Cancer: Recommendation Statement. Rockville, MD: Agency for Healthcare Research and Quality; 2004. Accessed at www.ahrq.gov/clinic/uspstf/uspstest.htm on 4 August 2010.

5. Bennett HF, Middleton WD, Bullock AD, Teefey SA. Testicular microlithiasis: US follow-up. *Radiology*. 2001;218:359–63. [PMID: 11161147]

6. Kawakami T, Okamoto K, Ogawa O, Okada Y. XIST unmethylated DNA fragments in male-derived plasma as a tumour marker for testicular cancer. *Lancet*. 2004;363:40–2. [PMID: 14723995]

7. Carmignani L, Gadda F, Gazzano G, Nerva F, Mancini M, Ferruti M, et al. High incidence of benign testicular neoplasms diagnosed by ultrasound. *J Urol*. 2003;170:1783–6. [PMID: 14532776]

8. Peterson AC, Bauman JM, Light DE, McMann LP, Costabile RA. The prevalence of testicular microlithiasis in an asymptomatic population of men 18 to 35 years old. *J Urol*. 2001;166:2061–4. [PMID: 11696707]

9. DeCastro BJ, Peterson AC, Costabile RA. A 5-year followup study of asymptomatic men with testicular microlithiasis. *J Urol*. 2008;179:1420–3; discussion 1423. [PMID: 18289592]

10. U.S. Preventive Services Task Force. Screening for testicular cancer. In: *Guide to Clinical Preventive Services*. Washington, DC: U.S. Department of Health and Human Services; 1996:153–7.

Where is that article I read in *Annals*?

Search archives
of *Annals* —
articles since
1927 available
for printing or
online reading

The screenshot shows the Annals of Internal Medicine website interface. At the top, there is a navigation bar with tabs for HOME, CURRENT ISSUE, PAST ISSUES, MOBILE, ABOUT, ACP, SUBSCRIPTIONS, E-MAIL ALERTS, and SUBMIT. Below the navigation bar, there is a search box with a search button and a dropdown menu for "Institution: ACP". The main content area features a "Early-Release Articles" section with a list of articles, including "National Institutes of Health State-of-the-Science Conference Statement: Family History and Improving Health" and "Systematic Review: Family History in Risk Assessment for Common Diseases". There is also a "Current Issue Highlights" section for November 2009. On the right side, there is a "User Name" login field and a "LOG IN" button. Below the login field, there is a "Search" box and a "LOG IN" button. At the bottom right of the screenshot, the text "AIM9010" is visible.

Interested? Go to www.annals.org

Current Author Addresses: Dr. Lin: Center for Primary Care, Prevention, and Clinical Partnerships, Agency for Healthcare Research and Quality, 540 Gaither Road, RM 6107, Rockville, MD 20850.
Dr. Sharangpani: Michigan Department of Community Health, 201 Townsend Street, Lansing, MI 48913.

Author Contributions: Conception and design: K. Lin.
Analysis and interpretation of the data: K. Lin, R. Sharangpani.
Drafting of the article: K. Lin, R. Sharangpani.
Critical revision of the article for important intellectual content: K. Lin, R. Sharangpani.
Final approval of the article: K. Lin.
Collection and assembly of data: K. Lin, R. Sharangpani.