

Family history doubles risk of venous thrombosis

Lynsey Alger

A positive family history more than doubles the risk of venous thrombosis, researchers have found.

The risk escalates further if the thrombosis occurred at a younger age and quadruples if more than one first-degree relative had the condition.

The researchers also reported a poor correlation between family history and genetic testing as an indicator of risk, suggesting as yet unknown genetic factors in the etiology of venous thrombosis.

Collectively, the findings reaffirm the value of history-taking as a risk indicator in the clinic: "Family history is such an easy and cheap tool, which tells you a lot about your risk," said lead author Ms. Irene Bezemer, Leiden University Medical Centre, the Netherlands.

Bezemer and colleagues' study looked at the contribution of family history as a risk factor for venous thrombosis. Blood samples and information pertaining to family history and environmental triggers were collected from some 1,605 patients with a first venous

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thrombosis and 2,159 control subjects. Participants were from the Multiple Environmental and Genetic Assessment of risk factors for venous thrombosis, a large population-based case-control study. [*Arch Intern Med* 2009;169(6):610-5]

Of the patients with thrombosis, 31.5 percent (505 cases) had a first-degree relative with a history of venous thrombosis, com-

pared to 17.3 percent (373 cases) of control subjects. A positive family history increased the risk of venous thrombosis by more than twofold (odds ratio [95% CI], 2.2 (1.9-2.6)). In those with more than one relative affected the risk was increased by up to fourfold ([95% CI] 3.9 (2.7-5.7)).

Positive family history continued to be associated with higher risk regardless of environmental or genetic risk factors. However, the risk of venous thrombosis increased as the number of risk factors increased; patients with an environmental and genetic risk factor plus a positive family history were 64 times more likely to develop thrombosis compared to those with a negative family history and no known risk factor.

Dr. Sanjay Nalachandran, from Tan Tock Seng Hospital (TTSH) in Singapore, commented that history taking had always been integral in the diagnosis of thrombosis, but

added that the study served to "cement and confirm" the role of positive family history in identifying a patient's risk.

Thrombosis in Asia has been increasing. "In the early 90s [in Singapore], the incidence was around 2 to 5 percent per 10,000 patients in hospital, now it is closer to 10 to 15 percent," noted Nalachandran, who is a consultant in general surgery at TTSH.

Taking a full and detailed history, accompanied by a high index of suspicion, can help treatment be instituted early and thereby decrease patient morbidity and mortality, he said.

As for as the role of genetics in determining the risk of venous thrombosis, Bezemer recommends caution. "I hope we will get better in using genetics to predict the risk of disease but, at this time, we shouldn't run to the lab too fast to do genetic testing, but ask for family history." **MI**

Age no barrier to continued cervical cancer screening

David Brill

Cervical cancer screening should not stop at age 50, even in women who have had several all-clears in the past, new evidence suggests.

An analysis of national data from the Netherlands found that older women were just as likely to develop cancer after three negative smear tests as younger women.

Previous studies had found that pre-invasive disease is rare in well-screened over-50s, prompting calls for screening to be stopped at this age.

The Dutch study, however, focused instead on the incidence of full-blown cancers. It included data from 445,382 women aged 30 to 44 at the time of their third negative smear, and 218,847 women aged 45 to 54. [*BMJ* 2009 Apr 24;338:b1354]

After 10 years of follow-up the cumulative incidence of cancer was similarly low: 41 per 100,000 in the younger age group, and 36 per 100,000 in the older age group ($P=0.48$).

The findings suggest that age should not be the decisive factor for early cessation of screening in well-screened women, said lead author Dr. Matejka Rebolj. They do not, however, provide a definitive answer as to whether it will ultimately prove worthwhile to continue universal screening after three negative tests.

"We cannot really say with these data whether you should continue screening or not. However we can say that if you're screening younger women, then in order to make your policy consistent you should continue screening women above the age of 50," said Rebolj, a postdoctoral researcher at the University of Copenhagen, Denmark.

"The next logical step would be to do a proper cost-effectiveness analysis to determine whether this low absolute level of risk does warrant further screening. Until then we should encourage women to continue screening at the regular interval recommended in each particular country."

Singapore oncologist Dr. Francis Chin praised the quality of the data, and said that the findings support a policy of continuing screening up to age 69.

"This study confirms the importance of screening in the age group over 50 years old, because the risk of cervical cancer after several negative smears is similar in older versus younger patients," said Chin, consultant radiation oncologist at the National Cancer Centre Singapore.

"The predilection of doctors has always been that screening and early detection is better than treating cancer in the later stages. These data confirm and validate this policy," he said.

Singapore's Health Promotion Board (HPB) agreed that the study supports the current guidelines of its CervicalScreen Singapore initiative, implemented in 2004. The program, which promotes screening every 3 years, will continue to focus on increasing its coverage of eligible women, said Dr. Shyamala Thilagaratnam, director, Healthy Ageing Division, HPB.

Several previous studies have proposed that cervical screening should stop at 50, notably a 1997 paper which found that only 1 percent of 23,440 previously screened over-50s had significant cytological abnormalities. The authors concluded that ending screening in this group could reduce anxiety and enable better allocation of resources to targeting higher-risk women. [*Br J Obstet Gynaecol* 1997 May;104(5):586-9]

The case against this argument, however, could be further strengthened by another recent paper, supporting the findings of the Dutch study. UK researchers, reviewing National Health Service screening records for 2 million women, found that two thirds of all the lesions detected in over-50s were found in women who had previously had negative smear results. Discontinuation of screening would therefore lead to the majority of important abnormalities being missed, the researchers say. [*Br J Cancer* 2009 May 5; Epub ahead of print]

Singapore physician Dr. Siew Wei Fong concurred with the conclusion that screening should continue beyond the age of 50, in light of the recent evidence. She added that she does not expect any change in screening practices at the Singapore Polyclinics, where she is senior family physician. **MI**

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consultant, department of urology, Singapore General Hospital, also urged caution in the use of PSA testing, stressing the need to select the right patients.

"We are quite clear that screening is not a goal for Singapore at this juncture. For people who are asking to be tested, the key words are risk stratification," he said.

"PSA can be used as a tool for early detection of prostate cancer in the right patients. But on the other hand it can be harmful too if used in health screening without understanding the risks of the patient group and the general health of the patient."

The 20 percent mortality reduction with PSA screening was reported in the European Randomized Study of Screening for Prostate Cancer, which included 162,387 men aged 55 to 69 from seven countries. They were assigned to PSA screening every 4 years on average, or to no screening. [*N Engl J Med* 2009 Mar 26;360(13):1320-8]

After a median of 9 years' follow-up, the adjusted rate ratio for prostate cancer death in the screening group was 0.8, as compared to the control group (95% CI, 0.65 - 0.98; $P=0.04$). The absolute risk difference was 0.71 deaths per 1,000 men -

meaning that to prevent one death from prostate cancer, 1,410 men would need to be screened and an additional 48 cases would need to be treated.

The second study - the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial - included 76,693 men aged 55 to 74, recruited at 10 US centers. Men were randomized to annual screening - with PSA for 6 years and digital rectal exam for 4 years - or to the control group. [*N Engl J Med* 2009 Mar 26;360(13):1310-9]

After 7 years' follow-up, there were 50 prostate cancer deaths in the screening group and 44 in the control group (rate ratio 1.13; 95 percent CI, 0.75 - 1.70). Ten-year data showed similar patterns but follow-up was only complete for 67 percent of patients at the time of publication.

Despite the lack of national recommendations, PSA tests are commonly offered as part of executive health screens, according to Kesavan. This situation need not change in light of the studies, he said, but he emphasized the importance of explaining the potential consequences before testing.

"It would place the patient in a quandary if it was not explained properly and then he had an abnormal test. Then to put that worry to rest it would require him to undergo a biopsy." **- DB MI**

The transatlantic divide: Key points

American Urological Association Best Practice Statement

- PSA testing should be offered to well-informed men aged 40 and above, who have a life expectancy of at least 10 years
- The decision to proceed to biopsy should be based primarily on results of PSA and digital rectal exam, but should also consider patient age, family history, ethnicity, comorbidities, prior biopsy history, PSA density, PSA velocity and free and total PSA levels
- Men should be informed of the risks and benefits of screening before undergoing biopsy

These revisions to the AUA statement, first issued in 2000, were announced at the recent AUA annual meeting in Chicago, US. For the complete statement, see www.AUAnet.org

European Association of Urology Position Statement

- Current data do not support adoption of population screening due to the large overtreatment effect
- Before considering screening, health authorities should assess cost-effectiveness, quality of life, overdiagnosis, overtreatment and current levels of opportunistic screening
- Experts should develop safe methods for noninvasive cancer surveillance
- New diagnostic markers and imaging modalities for prostate cancer are urgently needed

The EAU position statement was circulated by press release. For the complete statement, see <http://www.uroweb.org/press/press-releases/>