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Letter to Editor

Age limit for familial prostate cancer screening

Dear Editor

Prostate cancer is the second furthermost common cancer in men. About 288,300 men with prostate cancer in the United States and 1,414,259 prostate cancer patients in worldwide diagnosed in 2023 (1). Prostate cancer is influenced by race, genetics, and familial causes. Familial cases of prostate cancer usually occur at a lower age than sporadic cases. The maximum risk of prostate cancer in familial cases appears when at least two first-degree relatives have prostate cancer regardless of their age. Family history is also a significant risk factor for prostate cancer, although only a tiny proportion of cases will be due to high-penetrance genes (2-5). However, so far there have been no reports on the onset age of familial prostate cancer concerning the prostate cancer incidence time of close relatives (siblings) with prostate cancer in a family. There is also no report on the similarity of Gleason scores (between an individual and a family with prostate cancer) at the time of diagnosis.

Hypotheses: The most widely-used method for diagnosing prostate cancer based on the PSA change is a prostate biopsy. However, different age ranges have been reported in the studies for starting screening for prostate cancer (6). Also, the PSA level tremor is very challenging to start a prostate biopsy, leading to unnecessary prostate biopsies (7, 8). Therefore, this is a helpful method and harmful due to overtreatment and the complications of surgery due to the invasiveness of the method and the cost and stress imposed on the patient. Our clinical experience of over thirty years of dealing with the rearrangement of prostate cancer patients and the reported imperial data indicate that familial prostate cancer occurs in a range roughly corresponding to the age of the first-person tumor diagnosis. Moreover, the Gleason scores of the infected people in the family are the same at diagnosis. If proven (by measuring the consecutive PSA levels without limitations), it will reduce the stress on the patient, the cost imposed on the patient, and the complications of prostate biopsy surgery. It might also change the family screening protocol in people with familial prostate cancer, and it may lead to studies that focus on only a specific age range in each familial group, which reduces these destructive factors and provides a more accurate diagnosis of prostate cancer in a specific range.

Empirical data: According to the data available through clinical records, the age dispersions inside patients' families were much less than in the general population. Considering three families consisting of 3, 3, and 2 brothers, with the mean ages of 70, 67, and 67 years old, the corresponding standard deviations were 2, 2, and 1.4 years. In addition, the Gleason scores of these three families all ranged between 6 and 7 (table 1). The Phylogenetic information is drawn based on the three target families and probands of prostate cancer. The blue arrow indicates all Probands. Black shapes represent the affected members of prostate cancer (figure 1).

Evaluation: Assessing the hypothesis of family coherence in terms of age and Gleason scores, retrospective studies are needed to measure the corresponding distributions in a larger dataset consisting of brothers.

To implement this investigation, prostate cancer registries must be linkable to the identification data to explore familial relationships. In addition to the age and Gleason scores, other demographic and clinical covariates could also be extracted from the registries. Early diagnosis of prostate cancer can increase the chance of having successful treatment. The early diagnosis is dependent on early diagnosis (or downstaging) and screening. Prostate cancer early diagnosis depends on screening consisting of testing non-cancerous person to find tumor before of clinical symptoms. The range of screening ages for prostate cancer has increased over the last decades, but now we present a novel contradictory result of limiting the age of screening for prostate cancer in patients with a positive family history. We hypothesized that screening could be considered 3-5 years earlier than the typical onset age of prostate cancer incidence

in their family. We believe that the age and Gleason score of onsets in familial prostate cancer can provide critical background data for the exact age of screening. Similarly, it has been suggested that the screening age can be personalized in prostate cancer patients (9, 10).

Moreover, we suggest that clinicians consider the common Gleason score at diagnosis in their family. The same stage at diagnosis has been reported by Jansson F. et al. that suggests patients with brothers having a non-low-risk prostate cancer is more susceptible to the risk of more aggressive prostate cancer (11). A nationwide cohort study showed that prostate cancer in families in Sweden offers useful data for risk-tailored starting ages of prostate cancer screening according to the hereditary information (12). Medical information can be considered for evidence-based personalized prostate cancer screening (12).

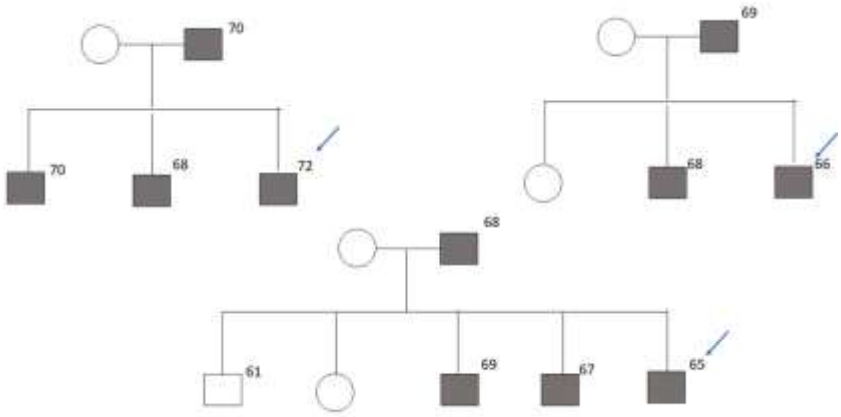

Figure 1. Schematic diagram of three different familial prostate cancer. The affected men are presented in grey rectangles. The age at diagnosis is written for prostate cancer patients and the current age for the non-cancerous person.

In several studies, it has been described in positive family history patients (especially having brothers with prostate cancer) the risk ratios (RR) increase about 2.5- 3.4 times in comparison with patients with an adverse family history and no prostate cancer positive family history. As the number of patients in affected family members increase especially in youngers, this risk even will be added (13).

Generally, the possibility of prostate cancer incidence increases gradually as age increases, from less than 25 cases per 100,000 persons in age ≤20 to about 350 per 100,000 persons aged from 45 to 49, to more than 1,000 per 100,000 people ≥60 (14, 15). So, the prostate cancer screening age based on most urology guidelines like AUA indicated starting no later than age 55 through PSA screening starts about ages 45–55 (16, 17). Based on the European Randomized Study of Screening for prostate cancer (ERSPC), the main age group is between the ages of 55–69 (18). Despite the noteworthy 21% relative prostate cancer death decrease in approval of screening, the reduction of the screening period is still considered pre-requirement because of the expenses and harms of screening. A recent population-based cohort study in Göteborg, Sweden, and Malmö has displayed that routine screening at 50–54 could decrease prostate cancer mortality by 17% at 17 years (19). The European Association of Urology (EAU), European Society for Radiotherapy & Oncology (ESTRO), and International Society of Geriatric Oncology (SIOG) suggest starting screening mostly at the age 50 for men, excluding men with a positive family history or Afro-Americans, that stating screening age decrease to age 45 (20).

According to investigators, having family first-degree relatives prostate cancer can be an alarm to start screening about 3-12 years earlier than the general population (9, 21). The same result was reported by Kohestani telling in positive family history of prostate cancer patients, the starting time of screening should be at least 12 years earlier than 50 years. Though, diverse patients can reached this threshold at dissimilar years, conditional on the number of their first-degree relatives with prostate cancer and the exact age of their relative cancer diagnosis (22). Meta-analysis supports

that having positive family history of prostate cancer especially in relative diagnosed with prostate cancer can be an important risk for upcoming prostate cancer growth (23-25). Before the PSA screening era, this consequence was mainly correct for the diagnosed disease through clinical symptoms appearance. The National Comprehensive Cancer Network (NCCN) and Memorial Sloan Kettering Cancer Center (MSKCC) Guidelines even support screening beginning at age 45 (26-28). Men younger than 55 years do not have exactly the less significant disease versus to older age person in Australia. A study by Danta over 598 prostate biopsies and 723 prostatectomies matched subjects indicated that PSA screening earlier than age 55 (29). It was shown that initial screening at early ages is not equal to the risk of over diagnosis, while stopping screening does (30). The long screening period can bring the worry of over diagnosis and overtreatment of prostate cancer (31-33). Using three different advanced mathematical algorithms of prostate cancer diagnosis and development by Draisma evaluate central times and the fraction of over-diagnosed cancers due to PSA screening (34). In conclusion, prostate cancer screening should start five years before the incidence age of prostate cancer in his brothers. The age and Gleason score of onsets in familial prostate cancer can provide critical background data for the exact age of screening and diagnostic stages.

Table 1. Information of three different familial prostate cancer

Family Member	Affected relatives	Age at diagnosis (years)	Tumor Stage (TNM)	Gleason Score
I	Proband	72	T1c	7 (3+4)
Ia	Brother	68	T1a	7 (3+4)
Ib	Brother	70	T1c	6 (3+3)
II	Proband	67	T2a	7 (4+3)
IIa	Brother	65	T1a	7 (4+3)
IIb	Brother	69	T1c	6 (3+3)
III	Proband	68	T1b	7 (3+4)
IIIa	Brother	66	T1c	7 (3+4)

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