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Does prostate cancer aggressiveness change with increasing age?

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Disclosures:

In the past 3 years, Dr. Rosenberg has been a member of a Speakers Bureau and served as consultant to Abbott Laboratories, Allergan, Inc, Astellas Pharma US, Inc, GlaxoSmithKline, Ortho-McNeil-Janssen Pharmaceuticals, Inc, SanofiAventis US, Schering-Plough, and Watson Pharmaceuticals, Inc. He has also been a member of a Speakers Bureau for Forest Laboratories, Inc, Novartis AG, and Pfizer Inc, and served as consultant to Hoffman-La Roche, Inc.

In the past 3 years, Dr. Froehner received lecture honoraries or meeting participation support from the following companies: AstraZeneca, GlaxoSmithKline, SanofiAventis, Apogepha, Pfizer, Novartis and Bayer.

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Summary

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7 With the continuously increasing life expectancy in many parts of the world, prostate
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9 cancer is likely to become an increasingly important health problem. As life
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11 expectancy in men increase, not only are they more likely to be diagnosed with
12
13 prostate cancer but also to live longer with the disease **resulting in a** risk of
14
15 **experiencing** tumor progression and of eventually dying from the disease. It is
16
17 unclear whether prostate cancers affecting younger individuals have a different
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19 biology compared with those occurring in the elderly. Considering the challenges of
20
21 demographic change, it may be important to answer this question in order to tailor
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23 optimal individualized treatment strategies.
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3 In the United States and many European countries, prostate cancer is the most
4 common non-dermatological malignancy in males [1]. Old age is a well-established
5 risk factor for prostate cancer. More than half of **incident** prostate cancer cases and
6 more than 90 % of deaths from prostate cancer occur in men aged 65 years or older
7 [2]. Since the life expectancy continues to rise in most developed countries due to
8 decreasing old-age mortality [3], men will be increasingly likely to live long enough to
9 develop **symptomatic or even fatal** prostate cancer. Prostate cancer in the elderly
10 therefore represents an increasingly important health problem. The relationship
11 between age and prostate cancer biology is, however, still subject to controversies
12 [4,5].
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29 **Data from randomized trials**

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34 In the European Randomized Study of Screening for Prostate Cancer (ERSPC),
35 prostate-specific-antigen-(PSA)-based screening was found to reduce the mortality
36 from prostate cancer **for the entire study population** by 20 % [6]. This effect was,
37 however, not **demonstrable for** study participants aged 70-74 years (the oldest age
38 group included in this trial), among whom the rate ratio for death from prostate cancer
39 in the screening arm was 1.26 (95 % confidence interval: 0.80–1.99) **compared to**
40 **no screening** [6]. **These** data suggests that men may not benefit from prostate
41 cancer screening beyond their 70th year of life.
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53 In the only currently available randomized trial comparing radical prostatectomy with
54 watchful waiting in men with clinically diagnosed prostate cancer, there were no
55 detectable differences in disease-specific and overall survival rates between both
56 treatment arms in the subset of men aged 65 years or older. Surprisingly, patients
57 aged 65 years or older assigned to the watchful waiting arm were less likely to
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3 develop metastases or to die from prostate cancer, compared with their younger
4 conservatively treated counterparts [7]. Concerning disease-specific survival and
5 metastatic progression, the survival curves in men aged 65 years or older **whether of**
6 **watchful waiting or surgery** were very similar to that in younger ones assigned to
7 radical prostatectomy.

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10 Subgroup analysis showed that the benefit of the radical prostatectomy was limited to
11 younger men and that watchful waiting resulted in worse outcomes **(concerning**
12 **metastatic progression and survival)** in patients younger than 65 years (compared
13 with the radical prostatectomy arm in this younger subgroup and to both treatment
14 arms in men aged 65 or more years). The authors caution that the study was not
15 designed to look at specific age groups and note that they have no data to judge
16 biologic **relevance** of this age **threshold**. They further noted that the effect was not
17 statistically significant. However, they did hypothesize that if the patients had reached
18 an advanced age, potentially lethal tumors were more likely of already having
19 metastasized and therefore being incurable [7]. Compared with younger patients, in
20 those aged 65 or more years undergoing watchful waiting, there was, however, a
21 decreased rate of metastatic and eventually fatal progression [7], calling this
22 hypothesis into question.
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48 **Results of observational studies**

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52 In a series of 412 patients with metastatic prostate cancer, young age was an
53 independent adverse predictor of disease progression and mortality [8] suggesting a
54 faster progression of metastatic disease in younger patients. If confirmed in different
55 samples, this finding could be an alternative explanation of the restriction of the
56 treatment effect to younger men in the cited Scandinavian randomized trial [7]. There
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3 are, however, also data showing poorer survival in elderly men with prostate cancer.
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5 In a recent study, the outcome of metastatic prostate cancer was scarcely modified
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7 by age, whereas in locally advanced non-metastatic (cT4N0M0) disease there was a
8
9 higher survival rate in younger men [9]. This finding led the authors to conclude that
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11 surgery offers better outcomes in this age group and should be offered as part of
12
13 multimodal therapy. No theory was offered as to why a benefit was seen [9]. **In**
14
15 **another recently published very large study, higher age was associated with**
16
17 **poorer prostate cancer-specific survival in univariate but not in multivariate**
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19 **analysis (after controlling for treatment modality and disease risk) [10].**
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23 In patients from the pre-PSA era, age was not associated with prostate cancer-
24
25 specific survival neither after radical prostatectomy nor after external beam
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27 radiotherapy or with expectant management [11]. Also in a recently published series
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29 of conservatively treated prostate cancer patients aged 65 years or older diagnosed
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31 between 1992 and 2002, the probability to succumb to their cancer within 10 years
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33 did narrowly not differ after subdivision into age groups [12]. Another study revealed
34
35 a higher progression rate and a lower disease-specific survival among patients who
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37 underwent radical prostatectomy at an age of more than 70 years, compared with
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39 their younger counterparts in univariate but not in multivariate analysis (after
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41 controlling for the less favorable tumor-related risk profile in the elderly cohort) [5].
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43 Among high-risk patients (those with a Gleason score of 8-10 or positive lymph
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45 nodes), impaired disease-specific survival rates were observed in elderly men,
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47 whereas there were no such differences in the lower risk subgroups [13]. Similar
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49 observations were made by d'Amico and co-workers after external beam
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51 radiotherapy for clinically localized prostate cancer where older age was associated
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53 with a significantly worse prostate cancer-specific survival [14].
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3 To further add to the controversy, several studies demonstrated an adverse impact of
4 higher age on prostate cancer progression rates after radical prostatectomy. After
5 radical prostatectomy, a decreased progression rate in men younger than 40 years
6 has been reported [15] as well as higher biochemical tumor control rates in men
7 younger than 50 years [16], aged 60 years or younger [17,18] and aged 70 years or
8 younger [19], respectively. Richstone and co-workers observed a higher proportion of
9 adverse tumor-related prognostic factors (Gleason score, clinical and pathological
10 stages) in men aged 70 years or older compared with their younger counterparts but
11 no differences in biochemical disease-free and cancer-specific survival rates [20].
12 Less favorable tumor-related prognostic factors but no differences in systemic
13 progression and prostate cancer-specific survival rates were made in another large
14 study [21]. In two series with narrowly 5.000 patients each tumors with adverse
15 prognostic criteria were also more frequent in elderly men [5,21], whereas smaller
16 studies did not reveal such differences [13,18].

41 **Explanations for the reported associations between age and prostate cancer** 42 **outcome**

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45 From the available data, identifying a consistent pattern of interaction between age
46 and prostate cancer aggressiveness is difficult. It is relatively well documented that
47 there is an increasing proportion of adverse tumor-related prognostic factors with
48 increasing age [5,10,20-22] and a majority of studies seem to suggest an adverse
49 impact of higher age on prostate cancer-related outcome [5,9,10,13-19]. However,
50 there is also some evidence for the opposite [7,8]. With the currently available data, it
51 is not possible to explain the surprising lack of efficacy of radical prostatectomy
52 versus watchful waiting in men aged 65 years or older in the Scandinavian
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3 randomized trial comparing radical prostatectomy with watchful waiting [7]. The
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5 different distribution of risk factors for disease progression and mortality between
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8 older and younger patients in some studies [5,20-22] might in parts be caused by a
9
10 greater probability of elderly patients with factors suggesting aggressive disease
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12 (higher PSA value, larger tumor volume, higher Gleason score) being recommended
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14 to undergo immediate active treatment (surgery or radiotherapy) instead of active
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16 surveillance or palliative care. Such selection effect might result in an enrichment of
17
18 higher risk tumors in elderly surgical or radiotherapeutic samples and, conversely, of
19
20 lower risk cancers in younger conservatively treated cohorts and **may not be**
21
22 **completely controlled for** during statistical analysis. PSA-based prostate cancer
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24 screening that identifies tumors with a particularly favorable prognosis may create
25
26 another bias creating an improved outcome in younger men. Whether there are in
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28 addition the described confounding factors intrinsic biological (tumor- or host-related)
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30 age-related differences is yet unknown [21].
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39 **Future studies**

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43 To obtain reliable answers to the question whether increasing age modifies the
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45 aggressiveness of early prostate cancer, more information from randomized trials
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47 would be desirable. Appropriately designed studies could investigate such issues as
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49 whether tumor progression rates are actually lower in elderly conservatively treated
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51 patients as the Scandinavian randomized trial [7] suggested or whether there are
52
53 subgroups who are at a high risk of progression and could benefit from immediate
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55 curative treatment also at an advanced age. Even randomized trials, however, might
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57 be affected by a selection bias caused by an earlier detection of cancers by
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59 screening in younger men and a preference of aggressive treatment in elderly
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3 patients with an adverse tumor-related risk profile. Despite randomization, such kind
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5 of selection might result in an enrichment of young low risk cases and simultaneously
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7 elderly high risk cases making comparisons between age groups difficult to interpret.
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10 11 12 **Conclusion**

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17 At present, identifying a consistent pattern of interaction between age and prostate
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19 cancer aggressiveness is difficult. Selection may have confounded particularly non-
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21 randomized studies. Randomized trials comparing competing treatment options in
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23 elderly men with early prostate cancer that are adequately powered to enable
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25 meaningful subgroup analyses to investigate the relationship between age and
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27 prostate cancer biology.
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Key messages

With the currently available data, it is difficult to identify a consistent pattern of interaction between age and prostate cancer aggressiveness.

Altogether, a majority of studies seem to suggest an adverse impact of higher age on prostate cancer-related outcome, there is, however, also some evidence for the opposite.

Currently, it is not possible to explain the disturbing lack of efficacy of radical prostatectomy versus watchful waiting in men aged 65 years or older in the Scandinavian randomized trial comparing radical prostatectomy with watchful waiting sufficiently.