In this issue, Chen et al. (1) report results from a nested case-control study that examines a CAG repeat region in exon 1 of the androgen receptor gene (AR) in relation to risk of prostate cancer. In contrast with most of the early reports (2–4), but consistent with several more recent reports (5–9), fewer AR CAG repeats were not associated with higher risk of prostate cancer. The study by Chen et al. (1), conducted within the Beta Carotene and Retinol Efficacy Trial, was based on 300 cases and 300 controls, and, thus, reasonably powered to observe a moderate-sized effect.

The biological rationale to study this polymorphic region in relation to prostate cancer, an androgen-dependent disease in its initial stages, is strong. This CAG repeat encodes a polyglutamine chain in the transactivation region of the AR (10), and longer polyglutamine chains hinder the transactivation activity of the AR in vitro (11). Moreover, the number of repeats have been shown to correlate with a number of androgen-related clinical conditions; specifically, a high number of repeats appears to adversely influence fertility and spermatogenesis (12), and bone density (13), and fewer repeats are associated with increased risk of baldness (14) and benign prostatic hyperplasia (15–18). The initial studies showing that fewer AR CAG repeats related to a higher risk of prostate cancer (2–4) supported the hypothesis that androgenicity influences the development of prostate cancer. These findings also offered some insight into racial differences in susceptibility for prostate cancer because high-risk groups such as African-Americans tend to have fewer AR CAG repeats, and low-risk groups in Asia have more repeats (10).

It is unclear why the earlier finding of an association between fewer AR CAG repeats and prostate cancer risk has been difficult to confirm. Because prostate cancer is a heterogeneous disease, it is important to seek explanations for the apparently discordant results. Twelve studies have provided some relevant data on the topic. Four studies reported a statistically significant inverse association between AR CAG repeat number and prostate cancer risk (2, 4, 19, 20). Two of these studies (2, 4), conducted in the United States, are notable in that they largely included cases diagnosed at relatively young ages, were conducted at least partly before widespread PSA screening, and found that the CAG association tended to be stronger for more aggressive or advanced prostate cancers. A study of mostly advanced, symptomatic prostate cancer cases conducted in China, where PSA screening is not conducted, found a statistically significant association for repeats <22 versus ≥22 (RR = 1.65; Ref. 19). Finally, a small study of 40 cases and 40 controls conducted in South Africa found an inverse association between AR CAG repeat number and risk of prostate cancer (P = 0.02), and among patients, those with aggressive disease had fewer CAG repeats (P = 0.02; Ref. 20).

Seven studies did not find an overall relationship between AR CAG repeats and risk of prostate cancer (1, 5–9, 21). A notable feature of these studies is that almost all of the cases were diagnosed during the era of PSA screening. Additionally, most of these studies examined various subgroups based on age, and a consistent finding was that AR CAG repeats appeared most relevant for prostate cancers diagnosed at younger ages. In all five of the studies that presented results stratified by age group, a modest association was suggested for the youngest age group, usually cases diagnosed before the age of 60 or 65. Comparing AR CAG repeats <22 versus ≥22 in the youngest age group, the RRs were: RR = 1.47 (3); RR = 1.72 (5); RR = 1.36 (6); RR = 1.48 (1); and RR = 1.08 for each decrement in CAG repeats (7). In contrast, no associations were observed in older age groups in all of these studies. Two other studies, also with overall null results, did not present results stratified by age but did find that younger cases tended to have a statistically significant higher frequency of fewer AR CAG repeats (8, 9). In another study, which did not have controls, younger cases tended to have fewer AR CAG repeats than older cases (P = 0.02; Ref. 22). Only one study did not show this pattern of an association among younger cases or age of diagnosis (21). In that study, only ~10% of cases were <60 years.

To summarize, some patterns emerge from the discordant results. First, the studies with the strongest support that AR CAG length repeat number influences prostate cancer are those conducted in populations with minimal PSA screening (2, 4, 8, 19, 20). Secondly, the cancers most strongly affected appear to have a relatively aggressive phenotype (2, 4, 7, 8, 19, 20). Thirdly, the prostate cancer cases that tend to occur at younger ages tend to be most strongly related to AR CAG repeat number (1, 2, 4, 6–9, 20, 22).

The relation between fewer AR CAG repeats and higher risk of aggressive prostate cancer in younger men suggests that
a heightened state of androgenicity directly influences a pool of relatively aggressive, early onset “androgen-driven” prostate cancers. Possibly, prostate cancers that tend to occur at older ages may be less driven by androgenicity and more related to pathologic processes such as oxidative insults, although androgens may play a permissive role. Although speculative, this “two pool” model is consistent with several observations. First, African-Americans, presumably exposed to higher androgenicity through shorter AR CAG repeats and higher testosterone at younger ages, are particularly susceptible to early onset, highly aggressive prostate cancer, but the rate differences with Caucasians diminish with increasing age (23). Secondly, some data suggest that dietary factors, including potential antioxidants such as lycopene, influence primarily prostate cancers that occur at older ages but not early onset cancers (24, 25). Finally, in animal studies, some prostate tumors appear to be driven primarily by androgens, but in other tumors, additional factors, such as oxidative damage, are critical (26).

Notably, the three factors modifying risk associated with AR CAG repeats (PSA screening, age-at-diagnosis, and aggressive phenotype) are inter-related. The use of PSA for screening increases profoundly the pool of relatively indolent cancers that are diagnosed at young ages. Before PSA screening, most cancers diagnosed at younger ages (e.g., before 60 years) were relatively aggressive cancers with generally severe consequences (e.g., mortality by age 70 years). Now, with widespread PSA screening, the cancers diagnosed include those that would not have progressed if untreated or would have progressed only years or decades later. In fact, now the vast majority of cases diagnosed before age 60 years do not lead to mortality by age 70 years. Thus, identifying the cancers influenced by AR CAG repeats may be difficult in populations with widespread PSA screening. To continue to make progress in the understanding of prostate cancer, future studies need to consider potential etiologic differences in prostate cancers diagnosed at diverse ages, and the complicating effects of PSA screening, which expand the pool of relatively indolent prostate cancers diagnosed at young ages.

References

Edward Giovannucci


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