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Clinical Oncology Update: Prostate Cancer

Recent Developments in the Epidemiology of Prostate Cancer

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The purpose of this review is to examine the implications of recent trends in prostate cancer incidence and mortality and to consider recent progress of epidemiological research on this disease. The incidence and mortality rates for prostate cancer are changing throughout the world at an accelerating pace. Much of the increase in incidence is related to changes in detection technology, but increases in mortality rates suggest other factors are involved. Recent research has focused on race-related difference, diet and related lifestyle exposures, the aetiologic significance of vasectomy and, patterns of familial aggregation. Continued monitoring of trends in incidence and mortality will be important as prostate cancer becomes a greater public health burden worldwide. Epidemiological research has identified several possible risk factors which may be useful for prostate cancer prevention and targeting high-risk individuals for early detection intervention. Additional research may confirm and refine understanding of prostate cancer aetiology. © **1997 Elsevier Science Ltd. All rights reserved.**

Key words: prostate cancer, diet, alcohol, tobacco, vitamins, vasectomy, genetics

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INTRODUCTION

PROSTATE CANCER has been an epidemiological enigma. Over an extended period of relatively stable patterns of incidence and mortality, many different suspected risk factors have been studied with few showing consistent or strong associations with the disease. In recent years, population rates of the disease have changed dramatically and opportunities to study prostate cancer aetiology have increased commensurately. Innovative epidemiological investigations of prostate cancer have become more frequent and, very importantly, replication of research by multiple investigators has become more common. As increased incidence has been a stimulus to research, the sources and significance of the increase have themselves become topics of inquiry. Herein, these recent trends in both patterns of occurrence and research on risk factors will be reviewed. The public health implications relating to trends in prevention and early detection will also be discussed.

MORTALITY RATES

Prostate cancer mortality exhibits considerable regional variability. Figure 1 illustrates the range of recent mortality rates observable in different countries [1]. The highest mortality rates are seen in Switzerland, Sweden and Norway. Intermediate rates are seen in such countries as the United States, United Kingdom, Hungary and Germany. Substantially lower rates are reported for the Asian region including Japan, Hong Kong and Singapore. Some of this variation may relate to differences in accuracy of mortality reporting and medical care, but the magnitude of the variation is too great to be wholly attributable to such artifacts.

In the United States, age-adjusted prostate cancer mortality rates have increased by 28%, from 20.5 to 26.3 per 100 000 in the last 35 years [2]. Estimates for the United States for 1996 are that there will be 41 400 prostate cancer deaths compared to only 14 941 in 1961. A similar pattern of rising prostate cancer mortality has been demonstrated in many other regions of the world with a 13% increase in mortality occurring in the U.K. between 1965 and 1985 [3]. During the same interval, mortality increased by 13% in Denmark, 10% in Japan, 5% in Australia and 8% in Canada [3].

INCIDENCE

Long-term trends in prostate cancer mortality and geographic variations are significant, but the recent changes in

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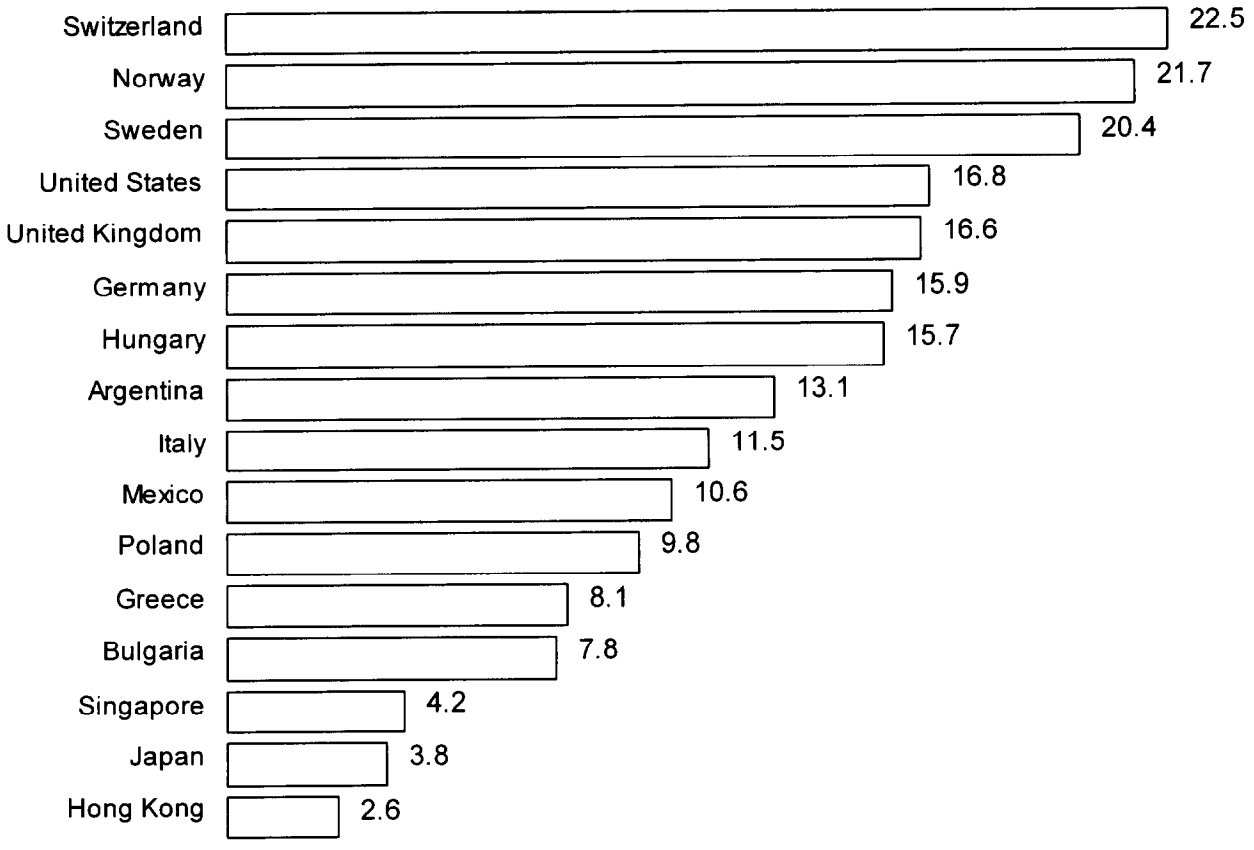

Figure 1. Selected international variations in age-adjusted prostate cancer mortality rates per 100 000 population, 1988–1991. Adapted from [1].

incidence are, by comparison, dramatic. Figure 2 illustrates the range of prostate cancer incidence rates evident worldwide [4]. Age-adjusted incidence in North America in 1985 was over 50% greater than for Western Europe, approximately twice that of Northern Europe, eight times that of Japan and fifty times that of China.

These differences noted in 1985 are probably more exaggerated now as incidence has sharply increased in the Western nations. Figure 3 shows the trend in prostate cancer incidence in blacks and caucasians in the United States over a recent two decade interval [5]. African–American men have substantially higher rates of prostate cancer compared to caucasians but both groups have shown markedly increased incidence. Between 1973 and 1992, rates in blacks increased 2.34-fold from 106.3 to 249.1 per 100 000. During the same period, rates for whites increased 2.91-fold from 62.5 to 181.9 per 100 000 men at risk.

INTERPRETATION OF RATES AND TRENDS

These very substantial temporal and geographic variations merit discussion in terms of both the clues they provide about the aetiology of prostate cancer and their public health meaning. With respect to aetiology, the international variations have been widely interpreted as supporting environmental and particularly, dietary mechanisms of causation. That variations may be attributable to exogenous factors rather than genetically determined predisposition is evidenced by the fact that risk appears to be modified by migration. For example, migrants to the United States from Japan eventually exhibit higher prostate cancer mortality than similarly aged persons who remain in Japan [6]. In addition, age-adjusted mortality rates in different countries correlate with variation in fat content of the region's typical diet and the long-term increases in mortality corresponds with a general pattern of increasing fat content in diets.

In contrast, the recent increases in incidence seem unrelated to any changes in the causal milieu. Most evidence indicates that these changes are largely attributable to changes in detection of prostate cancer. In the last 10 years, use of prostate specific antigen (PSA) testing and ultrasound guided biopsy has become widespread. Screening studies have shown these detection tools to be much more sensitive to the presence of prostate cancer than the previously most common prostate examination, digital rectal examination (DRE) [7, 8]. Potosky and colleagues [9] have correlated billing for these tests directly with increased incidence in the United States. In addition, studies based on hospital tumour registry data have shown a marked shift in the stage of disease at diagnosis toward earlier stage, asymptomatic disease, another indicator consistent with change in detection technology [10].

That the increased incidence of prostate cancer may be attributed to establishment of a new level of clinical sensitivity to the disease, rather than from the appearance of some new causal agent, may not diminish the public health significance of the rise. Patients diagnosed by whatever means require a physician's attention, at least further monitoring, and possible treatment and hospitalisation. The consequences in the United States have been documented in surveys by the American College of Surgeons [11]. As the number of patients with early, potentially organ-confined prostate cancer has increased, the number of patients trea-

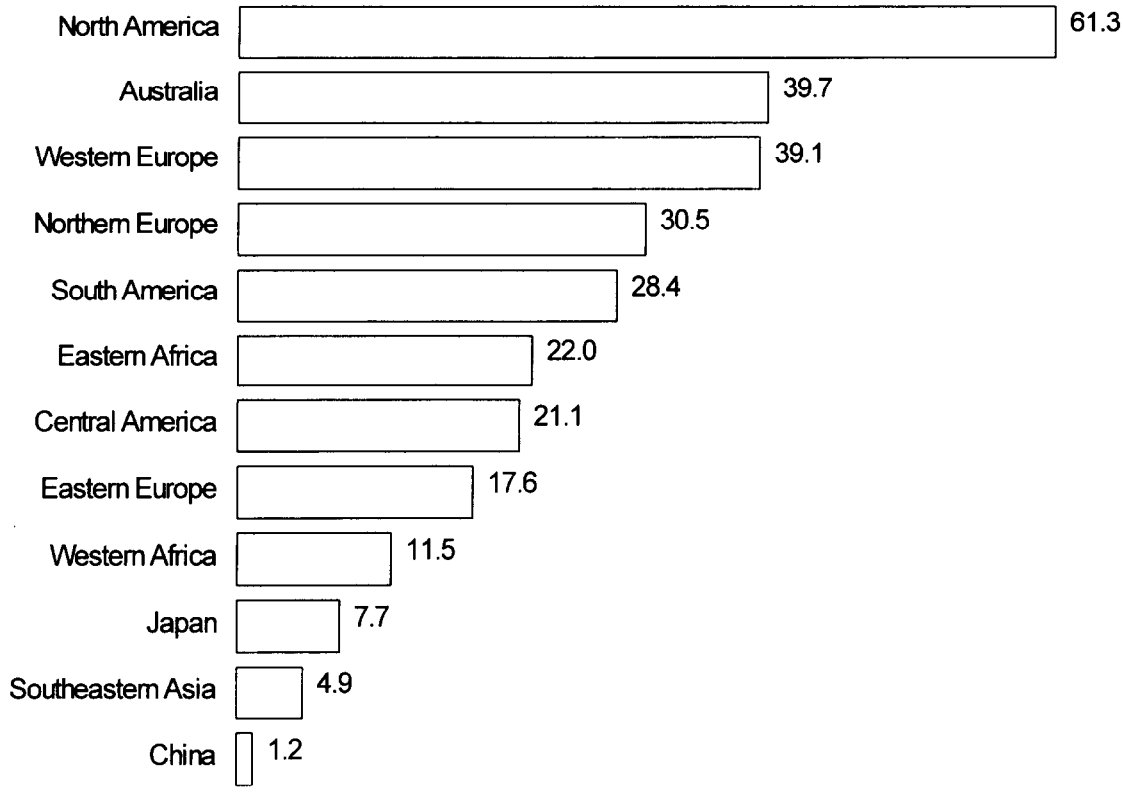

Figure 2. Selected worldwide regional variations in age-adjusted prostate cancer incidence rates per 100 000 population, 1985. Adapted from [4].

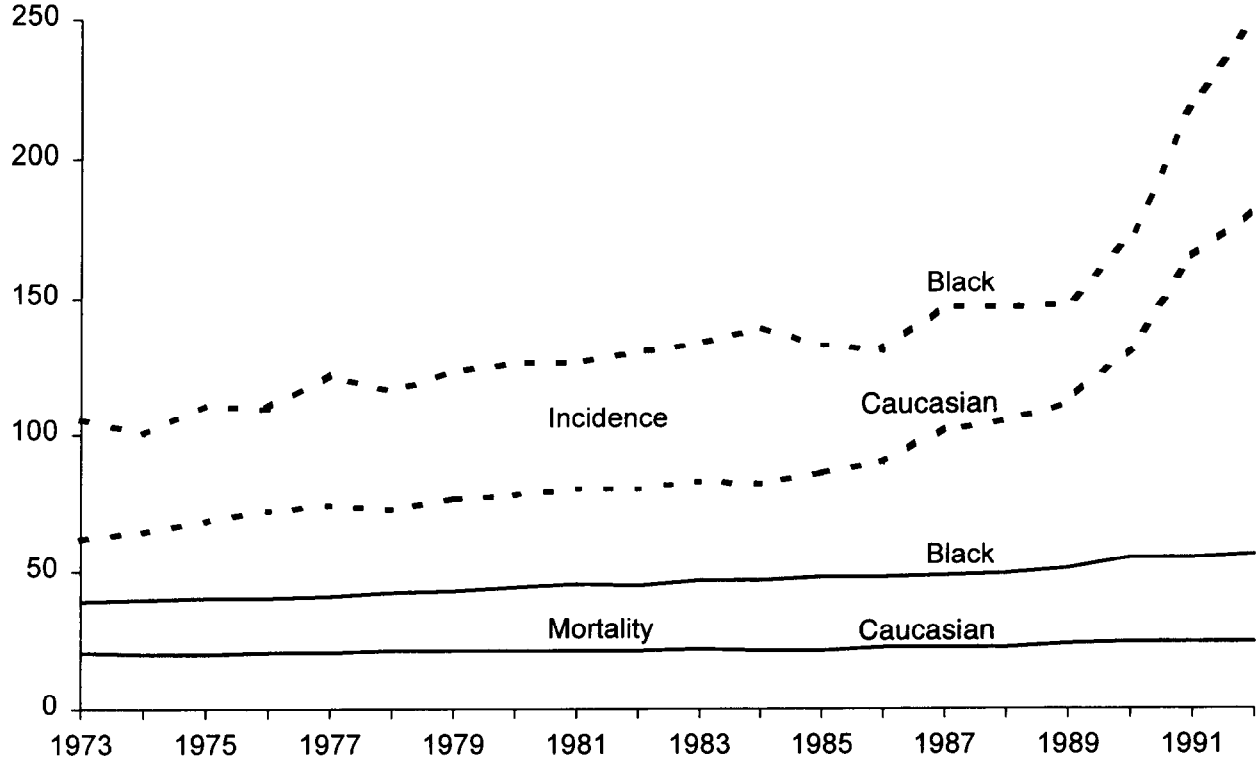

Figure 3. Trends in age-adjusted prostate cancer incidence and mortality rates per 100 000 in black and caucasian men in the United States 1973–1992 from the NCI Surveillance, Epidemiology, and End Results Program of the National Cancer Institute. Adapted from [5].

ted with curative intent has risen as well. The proportion of prostate cancer patients treated by prostatectomy rose from 9.9% in 1986 to 29.2% in 1993. Given the frequent occurrence of incontinence and impotency associated with prostatectomy, additional care is likely to follow initial intervention.

Although the yield and accuracy of prostate cancer screening has been documented, the benefit of increased prostate cancer detection in terms of either improved length or quality of life is not documented. Randomised clinical trials may not be feasible in light of the already widespread use of PSA testing in the population. Given the population-wide impact of early detection, close monitoring of population mortality rates may provide the earliest proof of benefit. Such large increases in incidence of early disease without subsequent declines in mortality would suggest very strongly the lack of benefit from early detection.

RACE AND ETHNICITY

Some of the regional and national variations cited above reflect the fact that prostate cancer varies widely between race and ethnic groups. African–Americans have the highest incidence rates with native Japanese having among the lowest. The reasons for these risk differentials are not understood but, dietary and other culturally mediated difference have long been suspected to play important roles. Recently, however, Ross and colleagues [12] have shown that biomarkers of 5-alpha-reductase activity are higher in caucasian and black men compared to Japanese subjects. 5-alpha-reductase may play a specific promotional role in prostate carcinogenesis by enhancing enzymatic conversion of testosterone to dihydrotestosterone (DHT), an androgen involved in normal and hyperplastic prostate growth. Race-related differences in 5-alpha-reductase activity explain geographic variations in risk not explained by environmental exposure and cultural differences. These epidemiological findings may also relate to the prospects for chemoprevention of prostate cancer. The drug, finasteride, is a synthetic inhibitor of 5-alpha-reductase and it has been shown to reduce levels of DHT [13]. Prevention trials are underway to further evaluate the potential of finasteride in inhibiting prostate cancer in men at high risk.

DIETARY

As noted above, variations in population rates and their correlation with dietary practices have supported the notion that dietary fat consumption may be related to risk of prostate cancer. These observations are, however, weak evidence for the association because so many other factors differ between populations at the same time. Furthermore, from these comparisons, there is little to confirm that the persons in the population with the greatest risk of disease are the same as those who have greater exposure to the putative cause. For these reasons, population rate comparisons and correlation very often are only suggestive, with stronger evidence requiring more rigorous epidemiological research.

There are other lines of epidemiological evidence available which support the notion that dietary fat intake is related to prostate cancer aetiology. Multiple comparisons of the self-reported diet histories of men with prostate cancer compared to control subjects have shown that the cancer patients tend to report greater consumption of foods high in fat content [14–16]. This association has been particularly evident when the focus is on animal fats. Meat and milk intake are food groups which have repeatedly been associated with risk elevation, but a role for other fat sources has been implicated in recent research on a large cohort of United States physicians [17]. Serum plasma specimens obtained up to 6 years before diagnosis showed fatty acid level elevations in those men who developed prostate cancer. Particularly related to risk was γ-linoleic acid from vegetable sources.

While there is some convergence of evidence, there is much about the role of dietary fat in prostate cancer aetiology that requires clarification. First, not all investigators have been able to demonstrate the dietary fat–prostate cancer risk relationship. In some investigations, the association has been weak and/or statistically insignificant [18–20]. Part of the inconsistency of results is possibly the product of the differences in research methodology, differences in the populations studied, and the inaccuracy of dietary recall.

Another possibility that might account for the elusiveness of the relationship is that dietary fat may be important in only a part of the diseases natural history. There is evidence, for example, that dietary fat may play a greater role in accelerating tumour growth than in initiating cancer. That the role of dietary fat is promotional is supported by the findings in some studies that the effect of fat intake is most evident, or only evident, when analysis is restricted to more advanced prostate cancers [21]. This is consistent with animal experimentation demonstrating that dietary fat reduction lowers the growth rate of implanted human prostate tumour [22]. A mainly promotional role for dietary fat also might explain the observation that prostate cancer found only at autopsy is less correlated with dietary variations compared to clinical prostate cancer.

Confirmation of a specialised, promotional effect of dietary fat intake could have important implications for management of the growing number of very early prostate cancers now being detected with aggressive screening. Dietary modification may be a useful adjunct to surveillance in persons diagnosed with low-grade, low-volume prostate cancer. Alternatively, dietary modification for persons at high risk due to a strong family history of prostate cancer might augment the current recommendations for frequent screening. Although the implications are intriguing, the available data on fat and prostate cancer cause or progression are not now sufficient grounds for any specific risk or disease management recommendations.

Other aspects of diet investigated epidemiologically include micronutrient intake and alcohol consumption. Interest in beta-carotene follows research on other cancers which suggested a protective role for this vitamin A precursor, obtained mainly through fruit and vegetable consumption. Results relating to prostate cancer, however, have been quite inconsistent, with some studies showing possible risk reduction [20] and others showing no relationship [28] or possible increases in risk [16]. When associations have been found, they have suggested only relatively weak relationships or have been found only in age-specific subsets. While the several studies focusing on beta-carotene provide scant evidence of a potentially important role in prostate cancer prevention, interest in other carotenoids has been recently generated by the results of prospective study of a large cohort of health professionals in the United States [23]. In that study, intake of tomatoes, tomato sauce, tomato juice

and pizza, significant sources of the carotenoid, lycopene, was associated with reduced prostate cancer risk. Given the mixed results from studies of beta-carotene, judging the significant of the role of lycopene probably should be deferred until these results can be replicated in other study populations.

Results from a lung cancer chemoprevention trial conducted in Finland has provided some unexpected indications that alpha-tocopherol (vitamin E) may inhibit prostate carcinogenesis [24]. A double-blind protocol involving administration of beta-carotene, alpha-tocopherol or placebo to nearly thirty thousand male smokers did not show lung cancer incidence reduction as hypothesised. There was, however, a 34% reduction in prostate cancer incidence associated with receiving alpha-tocopherol. The randomised clinical trial is perhaps the most rigorous type of research than can be conducted in human populations and the results from this study should stimulate further inquiry concerning the role of vitamin E in prostate cancer cause and prevention.

The geographical distribution of prostate cancer mortality in the United States has been interpreted as supporting the hypothesis that low levels of vitamin D are related to low sunlight exposure may increase risk [25]. This idea is further supported by analysis of vitamin D metabolites in sera stored before diagnosis for prostate cancer cases and controls [26]. The hypothesis, however, was not supported by the results of a study conducted by different investigators in a cohort of over twenty thousand United States residents [27]. Although the results from these biomarker studies are mixed, this approach is more rigorous than inferring vitamin D status from residence and presumed sunlight exposure and additional research on this topic is needed.

It is plausible that alcohol intake could affect prostate cancer risk by its influence on sex hormone metabolism. However, several large studies have failed, to uncover a significant association between self-reported alcohol beverage intake and prostate cancer risk [28–30]. This absence of effect occurred even when long-term and high level patterns of consumption were studied.

TOBACCO

Several studies of smoking habits and prostate cancer have shown little evidence of an effect for this exposure [7, 8, 29, 31, 32]. Important exceptions to this overall trend are from follow-up of two large cohorts in the United States. Nearly a quarter million military veterans were followed for 26 years following a survey of smoking habits [33]. Over four thousand subsequent prostate cancer deaths were identified. A statistically significant 18% increase in risk for a history of cigarette use was observed. Among men reporting heaviest cigarette use, there was a 51% increase in risk. Follow-up of over forty thousand health plan members in California identified 238 prostate cancers [28]. Reporting smoking one or more packs of cigarettes daily was associated with a statistically significant 1.9-fold increase in risk. While both of these studies have methodological limitations, their large sizes and prospective designs give them some advantage in rigor over the case–control studies which have been less supportive of a role for tobacco use. Cigarette smoking might have a biological role in prostate cancer carcinogenesis as a means of exposure to chemical carcinogens in tobacco smoke or by hormonal influence.

PHYSICAL ACTIVITY

Under the assumption that levels of physical activity may influence or reflect hormonal status, a few studies have examined this as a prostate cancer risk factor. Long-term follow-up of university graduates in the United States found significantly reduced risk among men who reported themselves highly physically active years prior to diagnosis [34]. There was no evidence of a dose–response relationship and the result was based on small numbers. A recent case–control study which included significant numbers of caucasian, black and Asian men found no risk reduction or increase related to the time the study participant reported spending in vigorous activity [35]. This negative result was uniform across the different groups studied. Occupations may be generally classified with respect to the level of activity they require and a study in Shanghai found prostate cancer to be more likely among men with more sedentary occupations [36]. Another study, conducted in Hawaii, found the opposite [37]. These studies are limited by the problem that occupation is only an indirect indicator of physical activity and it is confounded by the socio-economic and other correlates of job status. In light of the mixed evidence, it would seem that if physical activity has any role in prostate cancer aetiology, it is no more than minor.

VASECTOMY

The association of vasectomy to prostate cancer risk became a very important research topic following publication of three retrospective studies carried out in different populations in the United States [38–40]. In spite of the facts that vasectomy had generally been regarded as having no measurable long-term adverse health effects and numbers of men worldwide who had vasectomies for contraception was large and growing, these studies supported the hypothesis that vasectomy significantly increased prostate cancer risk. In one study, there was a 2.2-fold increase in risk associated with a vasectomy 13–20 years prior to diagnosis and increased risk was related to duration of the vasectomised state, with a dose–response relationship [39]. These initial studies, however, had not been designed specifically to test the hypothesis that vasectomy was related to prostate cancer and chance, bias or confounding could produce the appearance of risk where there really was none. Skepticism concerning the causal significance of the earliest epidemiological studies also arose from the lack of known biological mechanism which would account for the risk effect.

Several more studies of vasectomy and prostate cancer risk now have been reported. Some of the most carefully designed studies have failed to confirm overall increased risk related to vasectomy [41–43]. However, other well-designed studies continue to be reported, showing increased prostate cancer risk related to a history of vasectomy. Follow-up of 10055 United States health professionals who had vasectomy and 37800 who had not, revealed a 1.7-fold increase in overall risk and greater risk in men who had the vasectomy 22 or more years prior to diagnosis [44]. In 14 607 vasectomised men and an equal number with no history of vasectomy, identified through their wives' participation in a prospective cohort study, the overall increase in risk was 1.6-fold [45]. A small case–control study conducted in China found a 2-fold increase in risk associated with reporting vasectomy 10 years or more prior to diagnosis [46]. One recent study, which found no increased prostate cancer risk

related to history of vasectomy, surprisingly found altered endocrine profiles including lower serum concentration of sex hormone-binding globulin and a higher ratio of dihydrotestosterone to testosterone among vasectomised compared to non-vestectomised subjects [41]. The significance of these differences relative to any adverse health outcomes is unclear and these findings have not been subject to replication.

It is unlikely at this point that any individual study will definitively resolve the question of whether vasectomy is a risk factor for prostate cancer. The number of competently done investigations which have shown increased risk is too large for the hypothesis to be dismissed summarily. However, several studies have shown no indication of increased risk. This ultimately may prove to be an instance that exceeds the limits of epidemiological methods to answer public health questions. If a specific biological casual mechanism can be demonstrated in the laboratory or clinic, that mechanism and biomarkers of it can be the focus of population research. Such a study would represent a considerable methodological advance beyond the current state-of-the art.

FAMILIAL EFFECTS

Epidemiological findings concerning the increased risk of prostate cancer associated with family history of the disease have provided some support for the importance of genetic mechanisms in the causation of prostate cancer. Several studies have shown that a family history of prostate cancer confers significant increased risk to an individual [47–52]. Although the studies tend to report consistent findings with respect to the overall association, they differ with respect to several important details of the association such as the specific types of familial relationship involved, the ages at which risk is most evident, and the different types of cancers that may share the association. These relationship, age and site associated variations in risk may be related to the nature of the underlying biological mechanisms.

Breast cancer patients have been shown by different investigators to tend to report greater occurrence of prostate cancer family histories than do comparison patients [53–55]. A possible inference is that prostate cancer shares a linkage to the breast cancer gene *BRCA1* or some other genetic trait. The results of two recent investigations do not provide evidence that prostate cancer is linked to family history of any other cancer apart from prostate [56, 57]. In these studies, cases and controls did not differ in terms of the rates they reported family histories of any cancer other than prostate, of cancers of various organ systems, or colorectal, lung, breast or ovarian cancer. This absence of difference was in marked contrast to the relatively readily observed difference in reporting prostate cancer family history of cases versus controls, and may indicate that the genetic mechanism is specific to prostate cancer rather than associated with a cluster of cancer diagnoses.

Persons with a family history of prostate cancer represent a higher risk population who may benefit more from early detection intervention. Alternatively, the available data do not show that a family history of prostate cancer is a pervasive or necessary predisposing condition. In recent studies, fewer than 15% of unselected prostate cancer patients reported knowing of the same disease occurring in a first degree relative. Given the frequency that prostate cancer occurs without being diagnosed, it is likely a family history of disease is more common than may be reported by the individual. Even allowing for significant under-reporting, it remains probable that prostate cancer occurs in the majority of instances without significant familial predisposition.

Carter and colleagues [58] estimate that 9% of prostate cancer incidence is of the hereditary form of the disease. The importance of the hereditary mechanism, however, is difficult to assess in these data. In addition to the aforementioned problem of family histories unknown to the subject, there is the countervailing problem of environmental cause of the disease in persons with a reported family history. Related persons may share environmental exposures in addition to their genetic similarity. Similar dietary habits among closely related persons is an example of one type of environmental confounding that may play a role in this disease.

CONCLUSION

This review has been selective and some possible risk factors and older topics of interest may not have received any attention. This may prove to be an oversight because the aetiology of prostate cancer is not well understood and some factors overlooked herein may be shown in future research to be important. In spite of this limitation, it can be said from this review that there is some convergence of evidence that prostate cancer is a growing problem worldwide. Advances in detection technology have established a new clinical threshold and the number of persons who will require prostate cancer care will continue to grow.

As incidence and mortality has increased, some risk factors have become better understood. Epidemiological studies have tended to elevate the importance of race, dietary fat intake, and, familial predisposition. These same methodologies have left the role of vasectomy, micronutrient intake, cigarette smoking and physical activity unresolved. The ambiguous state of the data concerning these factors may be interpreted as demonstration of their minor importance if not complete insignificance. Epidemiological research on prostate cancer has been cumulative and continuing study of this disease may lead to discovery of means of prevention occurrence or progression of prostate cancer.

Alternatively, better understanding of risk factors may lead to better classification of individuals with respect to their personal risk. This could provide the information needed to make early detection and intervention for prostate cancer most effective.

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