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Global prostate cancer incidence and the migration, settlement, and admixture history of the Northern Europeans

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Abstract

The most salient feature of prostate cancer is its striking ethnic disparity. High incidences of the disease are documented in two ethnic groups: descendents of the Northern Europeans and African Americans. Other groups, including native Africans, are much less susceptible to the disease. Given that many risk factors may contribute to carcinogenesis, an etiological cause for the ethnic disparity remains to be defined. By analyzing the global prostate cancer incidence data, we found that distribution of prostate cancer incidence coincides with the migration and settlement history of Northern Europeans. The incidences in other ethnic groups correlate to the settlement history and extent of admixture of the Europeans. This study suggests that prostate cancer has been spread by the transmission of a genetic susceptibility that resides in the Northern European genome.

Keywords

Admixture; Prostate cancer incidence; Northern European; African; African American

Introduction

Prostate cancer is a chronic and progressive disease frequently accompanied by irreversible and lethal metastasis. Defining the etiology, so as to provide measures of prediction and prevention, is the utmost priority of prostate cancer research.

Prostate cancer is notorious for its varied geographic distribution across the world [1]. A rare disease in Asia and Africa, it is frequently diagnosed in other regions, especially in the West, where prostate cancer is viewed as an ageing-related malignancy preferentially occurring in certain ethnic groups [2].

The ethnic disparity suggests a role of inheritance in oncogenesis, and the impact of genetic risks on the development of prostate cancer is well recognized [3]. Firstly, inheritance of prostate cancer has been demonstrated by twin studies [4–8]. Compared to dizygotes,

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monozygotic twins have a significantly increased risk in both brothers. Secondly, prostate cancer occurs often within a family, and the family history is an empirical indicator in prostate cancer diagnosis. Segregation analysis revealed that males with a prostate cancer history in relatives of the first and second orders are more susceptible to the same disease [9–11]. Both paternal and maternal histories have similar predicting power, indicating an autosomal transmission [7, 8]. Thirdly, prostate cancer has a strong ethnic propensity. Prevalent among Europeans and African Americans, it is rare in Asians and Africans. Lastly, a fraction of the patients in the European, European American, and African American populations share two polymorphisms at chromosome 8q24, transmitted by admixture [12–14]. Genetically, prostate cancer is proposed to be a polygenic disease with alleles of low penetrance [15, 16].

The study of a genetics-based prostate cancer etiology is complicated by several seemingly contradicting facts. Firstly, although the seemingly random occurrence in a population may be due to the low penetrance nature, it could be alternatively explained by epigenetic mechanisms or by gene-environment interaction. Secondly, although African Americans are highly susceptible to prostate cancer, their African nations of origin have generally lower incidence [17– 22]. Thirdly, more prostate cancer cases have been diagnosed in recent years in nations that once had extremely low incidence. Given that the cause of the surge is not clear, socioeconomical, dietary, and behavioral changes have shown to be contributing risk factors, possibly by aggravating genomic susceptibility. Prostate cancer research has to offer a genetics-based etiology that could simultaneously address these conflicting epidemiologic observations.

The low penetrance of polygenic alleles would lead to a seemingly sporadic and age-dependent presentation of the traits, making it difficult to distinguish the genotypes from epigenetic influences. On the other hand, Mendelian inheritance makes the traits unique in certain ethnic group, which spreads the traits to other groups. Ethnic disparity of the incidence would indicate that the alleles have not yet been spread equally among other ethnic groups, and should be traceable based on the migration, settlement, and admixture history of the carrier.

We analyzed worldwide prostate cancer incidence data with respect to ethnic constituents of nations, and to the global migratory history of ethnic groups. This study revealed that the regional high incidence is associated with migration and settlement history of a certain ethnic group, which transmitted the susceptibility to other groups by admixture. This study suggests a straightforward strategy to identify the polygenic alleles.

Analyses

Since prostate cancer occurred frequently in certain ethnic groups, we compared the incidence among nations to determine whether it concurs with migration, settlement, and admixture history of the groups. Published data covering the last 10 years from cancer registries and incidence estimates from governmental and institutional sources were used. Related information was also obtained from publications, including those of the Descriptive Epidemiology Group of the International Agency for Research on Cancer of the World Health Organization, the National Cancer Institute of the U.S. National Institutes of Health, the American Cancer Society, and the Centers for Disease Control and Prevention of the U.S. Department of Health and Human Services. A consensus from various prostate cancer incidence databases is that the rate and trend for each nation remains relatively constant in the last decade. Among the databases, the GLOBOCAN 2002 provided cancer incidence in each nation in the year 2002, while GLOBOCAN 2008 had recently been released. To

simplify the presentation, we cite only GLOBOCAN 2002 data in this report, unless otherwise specified.

1. Assessment and election of the epidemiologic data

Besides the original rate (the crude rate), an age-standardized rate (ASR) is provided to facilitate international comparison, since prostate cancer is an ageing-related disease while life expectancies among nations vary. The ASR was a normalization of the crude rate with a "world standard age". Age standardization *per se* is a controversial issue, albeit a rational step, because it may actually lead to a distortion of the raw data [23, 24]. Before opting for etiological analysis, we assessed the impact of the age standardization, by examining the trend of changes from the crude rate to the ASR.

For many nations, the standardization with the "world standard age" introduced substantial alterations of the crude rate (Figure 1). It raised the cancer estimates for nations with shorter life expectancy, especially those in Africa, Central America, South America, and the Caribbean. On the other hand, the processing markedly reduced prostate cancer incidences in most of the developed nations. Sweden, for example, has documented a crude rate of 180.2 cases per 100,000 population at risk (180.2×10^{-5}), while the standardization yielded an ASR of 90.9×10^{-5}, an almost 50% reduction from a reliable surveillance datum [25].

Interestingly, almost all the nations with a reduced ASR are either in Europe or have a population majority of European origin. Except for Albania, all European nations have a reduced ASR, together with Australia, New Zealand, Canada, and the United States of America (USA). In South America, Uruguay, which has a population majority of European origin (88% white), has a markedly reduced ASR. The same is true for Puerto Rico (80.5% white) in the Caribbean. In Asia, the western-most Cyprus and Israel are the two nations with the highest and the second highest prostate cancer incidences, respectively, and both are assigned with reduced ASR. Comparing with developing nations, developed nations have advanced cancer surveillance and registry systems, and the crude rate therein reflects better the actual severity of the disease. The current standardization scheme has in effect negated large numbers of cases that are actually diagnosed in developed nations. Using the population structure of the developed nations should be able to alleviate the distortion.

To determine whether age standardization affects the drawing of a conclusion, we have performed two separate geographic epidemiological analyses using the crude rate and the ASR, respectively. We determined that even though it diminished the remarkable differences in prostate cancer incidences across nations, the current standardization strategy has not obscured the differences. At the global scale, a comparison with either the crude rate or the ASR still leads to similar conclusions. The ASR of the GLOBOCAN 2002 is used in this presentation.

2. European prostate cancer incidence and migration history of the Scandinavians

Genetic epidemiology has shown that inter-group breeding leads to spreading of disease alleles among ethnic groups [26–29]. In this sense, the geographic distribution of the varied frequencies reflects the migration, settlement, and admixture history of the susceptibility carrier. Analyzing the global non-uniformity in prostate cancer incidence, we examined the areal data, with the premise that the incidence reflects a susceptibility genotype, and the alleles are originated in the population of the highest incidence and spread through admixture.

A major source used to extract national information on ethnicity information for this analysis was the World Factbook 2002 (the U.S. Central Intelligence Agency, International Standard Book Number 0-16-067601-0). Information on the migration, settlement, and

admixture history of different ethnic groups was obtained from history textbooks and archeological and anthropological literature, and from online documents dealing with historical aspects of nations. The 2002 estimate for each nation's life expectancy at birth for males was extracted from The World Health Report 2004.

Globally, nations with the highest prostate cancer incidences are clustered in Northern Europe. Other nations with comparable incidences are Canada, the USA, Australia, and New Zealand (Figure 1), where population majority is of Northern European origin. In these nations, the indigenous Indians, the Aboriginals and the Maoris seldom contract the disease [30–32]. The high incidence thus co-migrated with the Northern Europeans, and the co-migration indicates a Northern European origin of the susceptibility. To trace further back to the genetic source, we first investigated the relationship between ethnic migration and the incidence of prostate cancer in Europe.

A gradient distribution of prostate cancer incidence is the salient geographic epidemiological feature in Europe (Figure 2). With the highest appearing in Sweden, high prostate cancer incidence spreads along the coast of the Northern Atlantic Ocean, declining gradually in the nations that are more distant from Sweden. In general, with Sweden as the apex, high incidence radiates southwestward, covering the west half of Northern Europe (*i.e.*, Sweden, Finland, Norway, Iceland, United Kingdom, and Ireland), all of Western Europe (*i.e.*, Germany, the Netherlands, Belgium, Luxembourg, France, Austria, and Switzerland), to reach the west part of Southern Europe (*i.e.*, Italy, Spain, Portugal, and Malta), with the incidence appearing inversely proportional to each country's distance from Sweden. On the other hand, the inland portion of Europe, Central and Eastern European nations, as well as those in southeast Europe, shows markedly reduced prostate cancer incidence, despite that they have a similar aerial distance from Sweden as the Western Europe nations.

This gradient of prostate cancer incidence has long been recognized. There has, however, not been a satisfactory explanation for the distribution. Paradoxically, Europe is a small continent and Northern and Western Europeans enjoy the highest standard of living with affordable medical care. Cause of the marked difference in prostate cancer incidence in this continent remains elusive.

Both in Europe and throughout the world, elevated prostate cancer incidences are mostly in coastal nations, suggesting that the susceptibility could have been transmitted through maritime routes. By studying the history of the various European ethnic groups, we identified a correlation between the geographic distribution of prostate cancer incidence and the migration, settlement, and admixture history of the Northern Europeans (Figure 2).

Southward migrations of the Northern Europeans are well known. Three successive waves of southward migration have been chronicled. During the Germanic Migration and Expansion from 750 BC to 600 AD, Germanic tribes in Southern Scandinavia settled in continental Europe and the British Isles. This was followed by the Norsemen Migration from 790 AD to 1090 AD. It happened that the Vikings, with advanced maritime navigation, traveled mainly along the coast of the North Atlantic Ocean, to the Mediterranean Sea. The Crusades from 1095 AD to 1272 AD brought large numbers of Northwestern European men to the Middle East. It is possible that at the end of the two millennia of southward migration, settlement, and admixture, the Scandinavian genetic attributes have been transmitted along the maritime routes. The attributes were relayed towards inlands, forming a Scandinavian genetic gradient in the present era. Importantly, this gradient is congruous with the geographic distribution of prostate cancer incidence, suggesting that the susceptibility is one of the genetic attributes that originated in Southern Scandinavia, and was admixed to other

European ethnic groups. Certain pedigrees of the Southern Scandinavians may bear a trait that renders susceptibility to the development of prostate cancer in late adult life.

Not only does the geographic distribution of prostate cancer incidence coincide with the migration routes of the Scandinavians, but the gradient of the incidence also reflects the extent of the Scandinavian settlements. Iceland, for example, is populated mainly with Scandinavians and is found to have a prostate cancer incidence comparable to Scandinavia. Historically a frequent migration and settlement place for the Scandinavians, the British Isles similarly have substantial incidences of prostate cancer.

Contrary to most of Europe, an opposite gradient appears in Iberia, where Portugal is seen with a higher prostate cancer incidence than its northern neighbor. Even though there is little literature comparing the Scandinavian influence on these two nations, Portugal could have acquired more Scandinavian influence. For a long time in history, especially in the Navigation Era, Portugal was a more prominent region for Northern European contact with Southwestern Europe. Profoundly, the imprint of the difference could be seen in the Americas, where former colonies of Portugal are seen to have higher prostate cancer incidences than the former colonies of Spain. The differential susceptibility between Portugal and Spain should have been established before 1494 AD, when the Treaty of Tordesillas divided the world between the two powers. Carrying a susceptibility inherited from the Scandinavians, the Europeans could have relayed it to other parts of the world through migration, settlement, and admixture.

3. Prostate cancer in the New World

With the recognition that the high prostate cancer incidence in Europe is a consequence of Scandinavian admixture, we traced a possible link between the Europeans and elevated incidences in other parts of the world.

It is easy to see that the high incidences in Canada, the USA, Australia, and New Zealand are correlated to European immigration and settlement, since these nations are resettled in recent historical times.

Large scale European migration to the New World started in the 15th century, 700 years after the Scandinavians settled in different parts of Europe. In the New World, emigrants from European countries often settle to regions where earlier emigrants from the same native land have settled. There is a close correlation between prostate cancer incidences in the New World and those in the European countries where the European Americans originated. In North America, most of the European Americans are originated from Northwestern Europe, where there are high prostate cancer incidences. In Central and South American countries, population majorities are descendants of the admixture between native Indians and Spanish or Portuguese colonists, who divided this region into two separate dominions. National prostate cancer incidences in Central and South Americas are much lower than in North America. It is interesting to notice that Brazil, a former colony of Portugal, has a higher prostate cancer incidence than nations of the former Spanish dominion. This corresponds to the situation in Europe, where Portugal has a higher prostate cancer incidence than Spain (Figure 2).

The Caribbean countries have a complicated history of colonization by European powers. Scandinavians and all the Western Europeans participated in the colonization. At the same time, many Africans were brought in by slave trading. During the Slave Trade era, admixture by the Europeans was extensive and complete. Many of the Caribbean countries now show high prostate cancer incidence.

4. Prostate cancer in Africans

Compared to Europe and the Americas, Africa seemed to have a much lower prostate cancer incidence in general. Prostate cancer incidence in African nations could be underestimated due to the lack of population-based cancer surveillance [33]. Prostate cancer is an aging-related disease, while most present-era African men do not enjoy a life expectancy comparable to that in developed nations. On the other hand, limited reports showed that elder African men may not be frequently afflicted with the disease or be detected to have elevated PSA [20–22, 34–39].

Furthermore, age standardization by both GLOBOCAN 2002 and GLOBOCAN 2008 failed to increase the incidence substantially, and the ASRs in African nations are still much lower than those in the developed world (Figure 1). Although the incidence estimates might not fully reflect the situation in Africa [40], and although the incidence there may be increasing, especially in nations along the Atlantic Ocean [17, 19, 41–44], it seems likely that compared to Europeans and Americans, native Africans are less susceptible to prostate cancer.

The low prostate cancer incidence is not evenly distributed in Africa. Some sub-Saharan nations, especially in West, South, and Central Africa, exhibit elevated incidences. The incidences have a general geographical pattern: the higher incidences being seen mostly along the Atlantic Coast, starting north from Mauritania, Guinea Bissau, and Sierra Leone and traveling south down to South Africa. In contrast, in the eastern half of Africa, along the Indian Ocean, many African nations have low incidences.

Since sub-Saharan Africa has a long history of human habitation, and Africa has experienced several population expansions and migration cycles [45], a founder effect should have been geographically noticeable if the susceptibility were passed down from ancestors of this continent. An association could not be made between the elevated incidence and a native ethnic group. The higher incidences along the Atlantic Coast and the interior encompass many ancestral tribes, while in the eastern half of Africa, nations with the same tribes do not show a higher incidence. The western Bantu migration, for instance, is thought to have expanded throughout southern part of the continent within the last 5,000 years. In the same region, however, distribution of prostate cancer incidence is in a mosaic pattern.

There is instead a correlation of the incidence to the history of European colonization. Following Portuguese ships' exploration of the Atlantic Coast, Northern Europeans began to settle in Africa in the early 17^{th} century along the same maritime route, starting from coastal regions to inland. More Western European nations participated in the "Scramble for Africa". Relative to their conquest of the Atlantic Coast, Europeans traveled much less along the coast of the Indian Ocean. The migration and settlement history of the Europeans superimposes on the geographic distribution of the elevated prostate cancer incidences, suggesting that admixture plays a role.

The duration of colonization and scale of European settlement seems to influence the elevation of the incidence. South Africa is one of the regions settled early on by the Europeans, and it has the highest prostate cancer incidence of all the African nations. In contrary, Ethiopia had only a brief history of European presence, and it has the lowest incidence, despite bordering nations having higher incidences. It is likely that prostate cancer has been transmitted to Africans through admixture.

5. Prostate cancer in African Americans

The high prostate cancer incidence in African Americans is a puzzling issue. Most of their African contemporaries in Africa are much less susceptible to the disease. Nonetheless, the

fact that family history is a strong risk factor for African Americans implies that prostate cancer is an inherited disease in this population. Since African Americans could not have inherited it from their African ancestors, they should have contracted the susceptibility from another source.

While European admixture in Africa is regional and transient, the European admixture with African Americans is complete and permanent. In the Americas, gene flow has been mainly from Northern Europeans to African Americans [46, 47], present-day African Americans carrying a substantial amount of the European genome [48]. The susceptibility to prostate cancer could have been transmitted to African Americans by admixture.

Simple Mendelian transmission of susceptibility alleles increases the susceptibility in the recipient population, but the incidence in the recipient would not surpass that of the donor unless additional additive or synergistic factors exist. If they inherited the susceptibility from Europeans, African Americans should have an elevated prostate cancer incidence well above native Africans, but lower than or at most equal to the Northern Europeans. With this rationale, we compared prostate cancer incidence between African Americans and European Americans (Figure 3). It is interesting to find that, when the crude rates are used in the comparison, African Americans in most States in the USA have a lower prostate cancer incidence. Especially in the states of Arizona, Iowa, Minnesota, Nebraska, Oregon, and Rhode Island, prostate cancer incidences of African Americans are remarkably lower (Figure 3). When the ASR is compared, however, every state shows an increased prostate cancer incidence in African Americans, most of which are much higher than Caucasians (Figure 3).

Three possibilities could be used to explain the discrepancy. First, similar to the global disparity between crude rate and ASR (Figure 1), the age standardization has exaggerated estimates in African Americans. A complete admixture of dominant attributes could result in similar incidences between the donor and the recipient population. Second, the African genetic background contains certain traits additive or synergistic to the received susceptibility. Third, exogenous factors unique to African Americans have interacted with the received susceptibility and have enhanced its penetrance. Additional scrutiny of the epidemiologic data and detailed genetic analyses are needed to elucidate the true mechanism.

DISCUSSION

The geographic distribution of prostate cancer incidence in Europe shows that susceptibility to prostate cancer is closely associated with the migration and settlement history of Scandinavians. Subsequently, susceptibility was transmitted to other parts of the world through the migration and settlement history of Europeans (Figure 4). The validity of this conclusion relies on the accuracy of the surveillance data, and global prostate cancer estimates are known to be variable in accuracy [33]. The high incidence in developed nations may reflect over-diagnoses in their cancer registries, whereas the low estimates for developing nations could be attributable to lack of cancer registration. The impact of cancer registration on the disparity in global prostate cancer incidence can only be determined after improved cancer registration measures in developing nations reveal the true prostate cancer burden. In this respect, GLOBOCAN 2008 showed elevated prostate cancer estimates in many developing nations [33], albeit the global disparity persisted. Meanwhile, a marked disparity remains in prostate cancer incidence among developed nations, even though they have advanced cancer registry systems. Similarly, a marked disparity exists among developing nations with less sophisticated registries. These disparities are in agreement with

the clinical observation that different ethnic groups have different susceptibility to prostate cancer.

With these caveats, this study may impact prostate cancer etiology research in two significant ways: it suggests that genetics plays a determining role in prostate cancer oncogenesis, and it points to a straightforward strategy to identify the underlying genetic elements.

Previous findings support the idea that a genetic susceptibility will be transmitted from one group to another as long as these groups acquire geographic adjacency. Northern Europeans are predisposed to unique diseases such as cystic fibrosis and idiopathic hemochromatosis. The respective Northern European alleles are found in other ethnic groups due to admixture [27–29, 49–51]. The geographic distribution of the ΔF508 cystic fibrosis allele in Europe is similar to that of prostate cancer incidence, and the allele has been transmitted to African Americans and Latin Americans. A recent genome linkage scan study has defined two alleles at chromosome 8q24 that are associated with an increased prostate cancer incidence both in Northern Europeans and in African Americans [12–14]. Frequency of these alleles in native Africans and other ethnic groups is low, suggesting transmission by admixture between Europeans and African Americans.

The results from our analysis display a hidden potential of prostate cancer. Because admixture causes spreading of susceptibility alleles, because these alleles have already been admixed to other ethnic groups, and because inter-group breeding is an aspect of globalization, global prostate cancer incidence is projected to increase, more obviously so in regions where prostate cancer has been a less frequently diagnosed malignancy. The surge of prostate cancer incidence in these regions will be persistent in the future.

Linkage analyses have concluded that prostate cancer is a multigene disease [15, 16]. Multiple chromosomes in certain Northern European pedigrees may be harboring susceptibility alleles, which may have additive or synergistic effects. On the other hand, these alleles are not deteriorating mutations, but underlie specific traits. Prostate cancer patients exhibit no detectable defects in embryonic and neonatal development or functional abnormalities. These alleles may be polymorphisms with antagonistic pleiotropy: ensuring successful reproduction but causing oncogenesis in later life [52–55]. Because alleles may be either in coding regions or in non-coding sequences [56, 57], and non-coding part of the genome is integral to phenotypes [58, 59], minimal unit for a susceptibility allele could be a chromosomal segment, the function of which is more complicated than a coding region. In this sense, it is the summation of the functional behavior of the linked European chromosomes that substantiates the prostate cancer susceptibility.

The results of our analysis support a genetic approach to the identification of the susceptibility alleles. Whereas admixture may transmit chromosomes from one ethnic group to another, probably in a random fashion, prostate cancer patients should all carry European chromosome components harboring the susceptibility alleles. The patients in Africa and Asia, and in the indigenous peoples in America, Australia, and New Zealand should share common European chromosomal components [18, 60]. Simply defining the minimal European chromosomal components shared among patients of different ethnicity could be an efficient approach to a comprehensive isolation of the susceptibility alleles. The case-only mapping by admixture linkage disequilibrium will be a straightforward strategy [61]. Detecting the minimal European chromosomal components may be a powerful method to predict, at birth, the risk for developing prostate cancer in later adulthood. The prediction at young age may provide an early opportunity to prevent prostate oncogenesis, because the disease mostly occurs in later adult life, and because the alleles have low penetrance.

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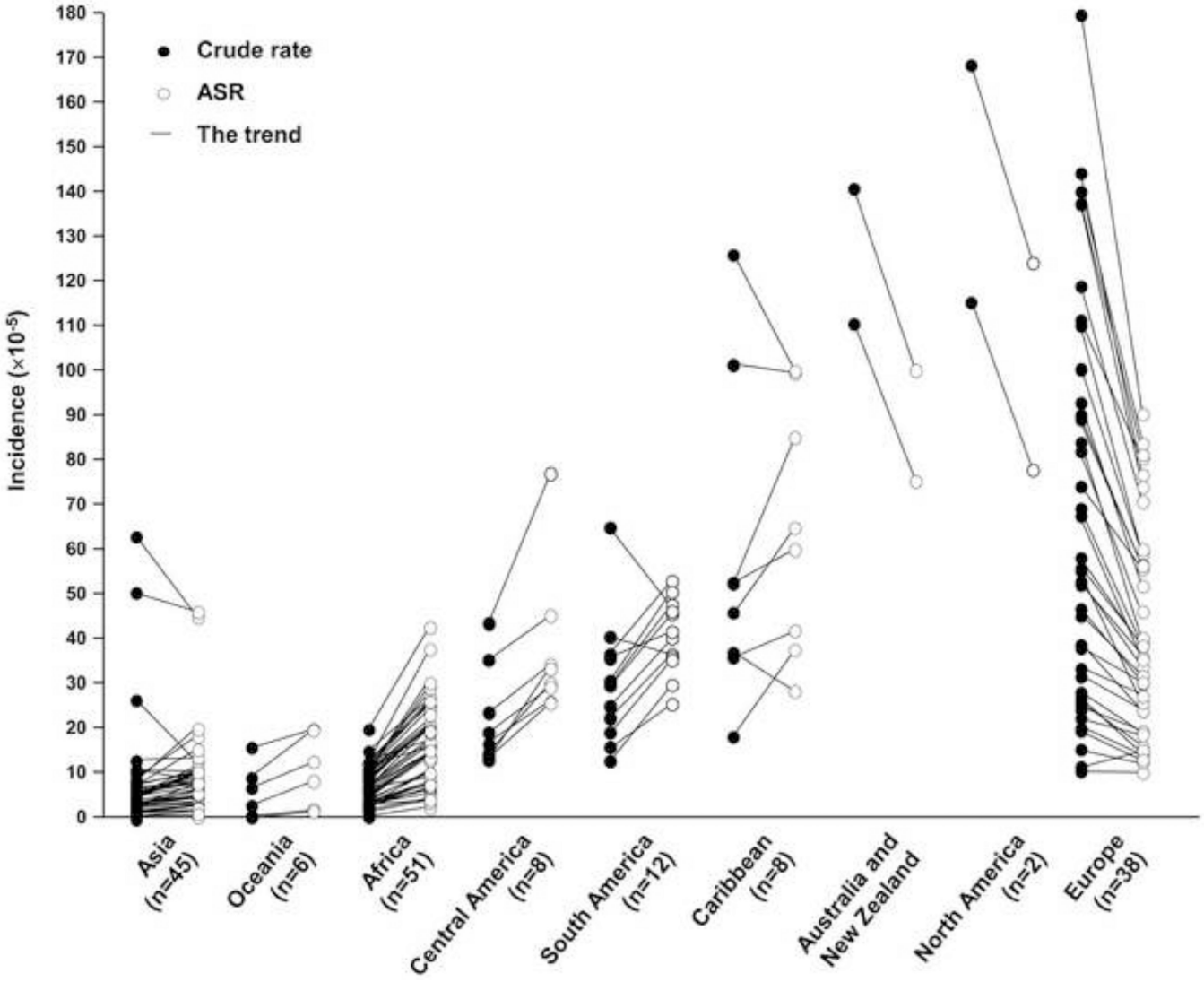

Figure 1. Changes in prostate cancer incidences caused by age standardization

Prostate cancer incidences in GLOBOCAN 2002 are analyzed. The trend of the change in crude rate and ASR for each nation is shown with a line connecting the two rates. Number of nations (n) in each region used in the analysis is indicated in brackets.

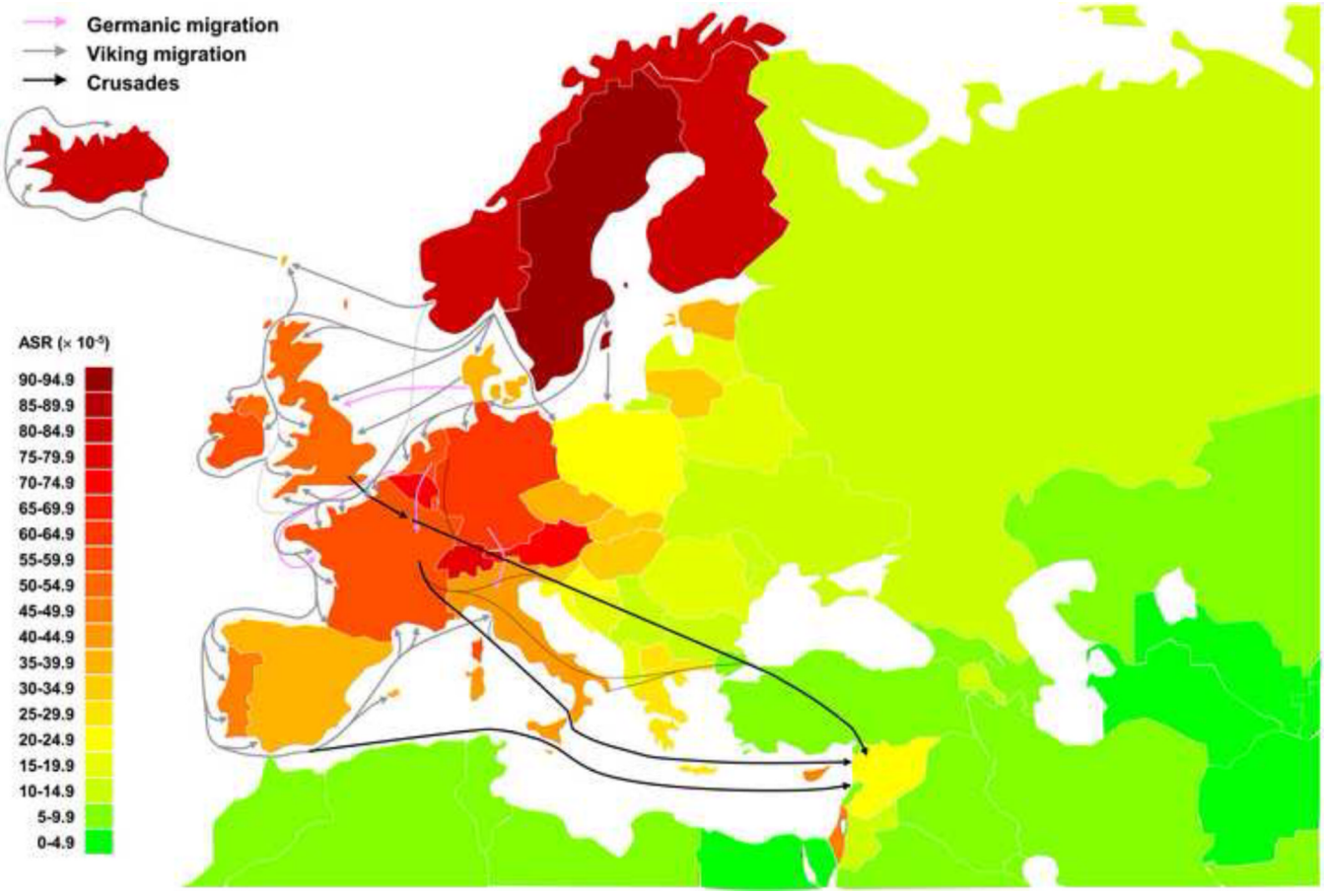

Figure 2. Southward migration and settlement of the Northern Europeans

In this schematic presentation, migrations of Scandinavians within Europe are plotted together with national ASR of prostate cancer incidence. Three successive waves of migration are indicated by arrowed lines, and the ASR for each nation is plotted according to the spectrum. It is known that migration of the Scandinavians was largely through maritime routes. Although migration *via* inland water passages in the Baltic States and Poland has been documented, it was on a small scale compared to coastal migration, and is not shown. For some nations and regions, there are no prostate cancer incidence data available for this analysis, and these areas are enclosed with solid lines and left blank.

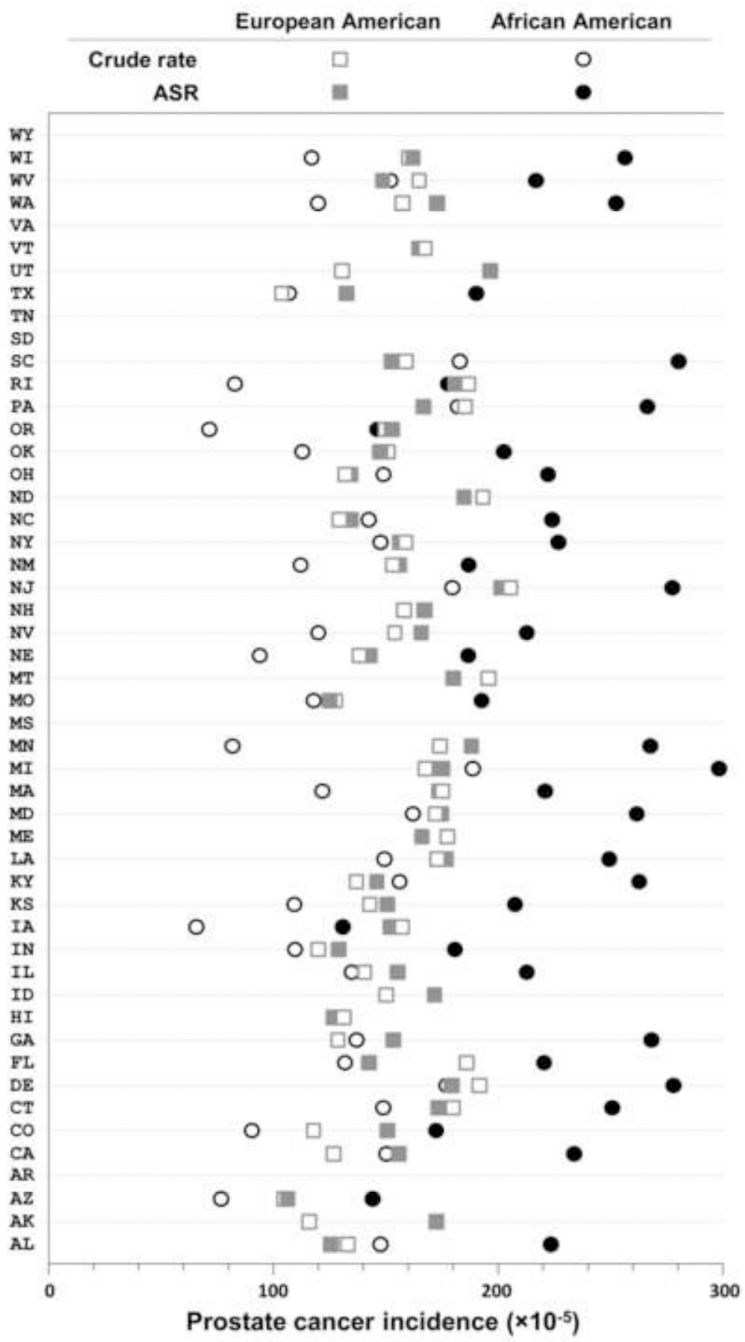

Figure 3. A comparison of prostate cancer incidences between African Americans and European Americans in the USA

United States Cancer Statistics Data – 2002 is used in this comparison. For each State (Y axis), crude rate of European Americans is denoted by grey open square, and ASR by grey filled square. Crude rate of African Americans is shown with open circle, and ASR with solid circle. For the year 2002, prostate cancer incidence data for several states (AR, MS, SD, TN, VA, and WY) are not available. In some other states (AK, HI, ID, ME, MT, NH, ND, UT, and VT), the population of African Americans at risk was too small to deduce a prostate cancer incidence.

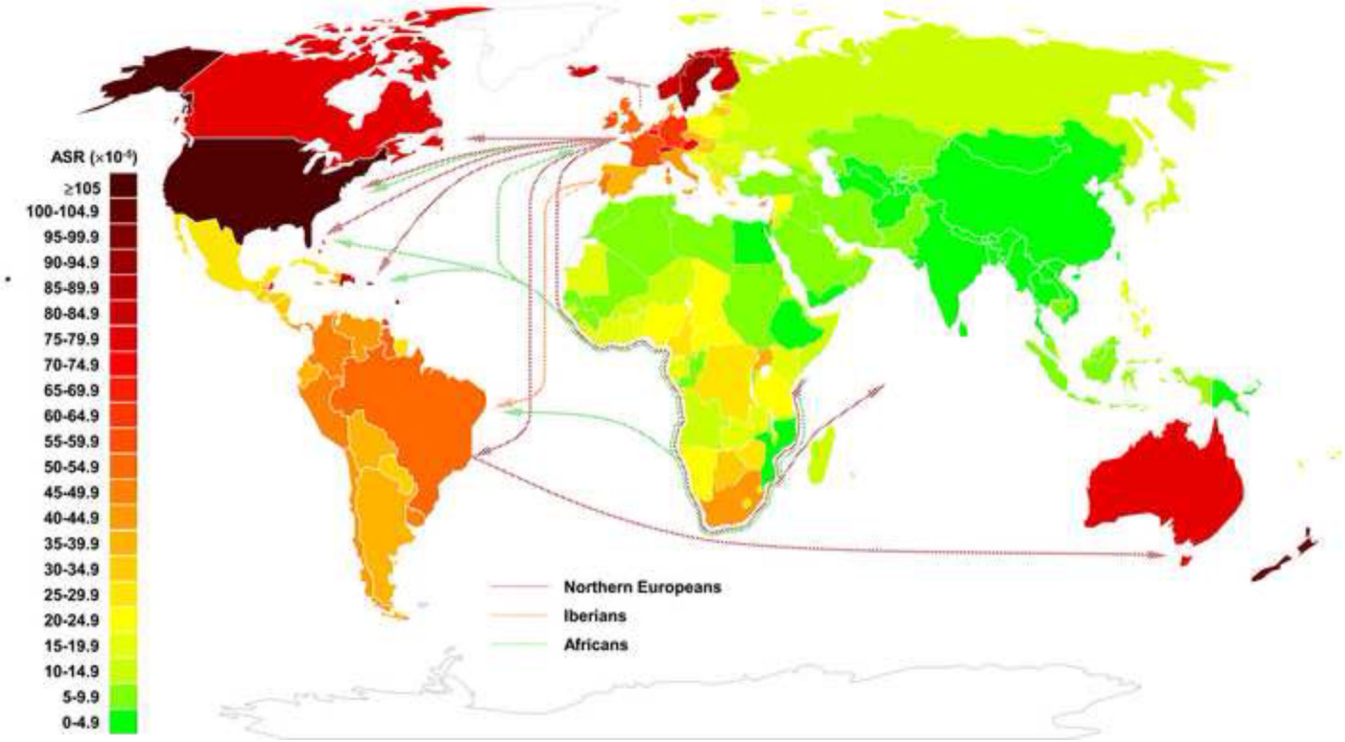

Figure 4. Global superimposition of prostate cancer incidence and the migration and settlement history of Europeans

The major routes of global European migration and settlement are plotted together with national prostate cancer incidences. Routes of European migration are marked with orange and red lines, and the direction of the slave trade from Africa with green lines. Prostate cancer incidence in ASR is plotted according to the spectrum. For some nations and regions, there are no prostate cancer incidence data available for this analysis, and these areas are enclosed with solid lines and left blank. Navigating through the Indian Ocean, Europeans also migrated to the Far East, especially to the coastal nations there. The scale of that migration has been small and the route is not plotted.