INTRODUCTION

Abdominal aortic aneurysms are responsible for a substantial public health burden in developed countries. In 1991, abdominal aneurysm was cited as the primary or secondary cause of 12,711 deaths in the United States (1). Aortic aneurysms of unspecified site, many of which were probably abdominal, were cited for a further 4,108 deaths. It has been estimated that abdominal aneurysms cause 1–2 percent of all deaths among men over the age of 65 in the United States (2). In Canada, vital statistics data show that there are approximately 1,000 deaths attributable to abdominal aneurysm annually (3). Since abdominal aneurysms often escape clinical detection, these vital statistics data probably underestimate the true magnitude of mortality related to abdominal aneurysm.

Abdominal aneurysms are also responsible for considerable morbidity and health care costs. In the United States in 1992, abdominal aneurysm was cited as the primary diagnosis for approximately 53,000 hospital discharges, and there were approximately 40,000 surgical operations for this aneurysm (1). In Canada in 1990, abdominal aneurysm was cited as the primary diagnosis for 5,638 hospitalizations (3).

Mortality and morbidity related to abdominal aneurysm has increased substantially in recent decades. In the United States, the number of deaths due to abdominal aneurysm increased by almost 20 percent between 1979 and 1991, and the number of related hospitalizations more than doubled (1). In England and Wales, the number of deaths due to abdominal aneurysm increased by 53 percent between 1974 and 1984 (4). In Canada, the number of hospitalizations related to abdominal aneurysm increased almost fourfold between 1970 and 1990 (3). Similarly, in Western Australia, the number of surgical operations for abdominal aneurysm more than doubled between the early 1970s and the early 1980s (5).

Despite the public health importance of abdominal aneurysms, much is still unknown with respect to their etiology. Historically, they have been considered simply a manifestation of atherosclerosis (6–8). However, this conventional theory has come under increasing challenge in the past two decades. Whereas aortic atherosclerosis is common, a relatively small proportion of persons develop aneurysmal disease. Furthermore, epidemiologic, genetic, and biochemical research indicates that the etiology of abdominal aneurysm is distinct from atherosclerosis per se.

The first part of this review provides an overview of the definition, pathophysiology, and natural history of abdominal aneurysm. In the second part, descriptive and analytic epidemiologic studies are reviewed with an emphasis on their implications for etiology.

LITERATURE SEARCH

In preparation for this paper, a review of the English-language scientific literature was conducted. This was performed primarily by searching the MEDLINE® databases for the time period 1966 through December 1998. Keywords used in the search included “aneurysm,” “aorta,” and “aortic aneurysm.” In addition, a search was performed using “aneurysm” as a Medical Subject Heading. The bibliographies of articles found through the MEDLINE® search were also searched for relevant articles.

BACKGROUND

Definition and classification of aortic aneurysms

An aneurysm is a localized dilation of an artery. It was described in 1581 by Fernel as “…the dilatation of an artery full of spirituous blood” (9). True aneurysms involve the dilation of all three layers of the arterial wall: the intima (the innermost layer facing the
lumen), the media (the middle layer), and the adventitia (the outermost layer) (8, 9). False aneurysms do not involve the dilation of all three layers of the arterial wall but rather are due to a disruption of the arterial wall (9). A dissecting aneurysm is a particular form of false aneurysm that most often results from the degeneration of the arterial media, tearing of the intima, and subsequent development of a hematoma in the arterial wall (10).

Most aneurysms occur in the aorta, and most aortic aneurysms occur in the infrarenal abdominal aorta. Studies from various populations have shown that 90-95 percent of abdominal aneurysms involve the infrarenal aorta (11-14). Etiologically, most aortic aneurysms are classified as “acquired,” distinguishing them from aneurysms that result from genetic diseases such as Marfan’s syndrome and Ehlers-Danlos syndrome. Historically, the large majority (>90 percent) of acquired aortic aneurysms were etiologically designated “atherosclerotic,” based on the common pathologic finding of coexistent atheromatous lesions and the absence of other obvious specific etiologic conditions (15). However, current reporting standards recommend that these aneurysms be classified as “nonspecific” until their etiology is more clearly defined (16).

Pathophysiology of abdominal aneurysm

Dobrin has described the development of an arterial aneurysm as a “...classic case of material failure” (17). The primary structural elements of the aortic wall are elastin and collagen (6, 18). Fibers of distensible elastin are arranged in concentric laminae in the aortic media, forming the primary load-bearing structure of the aortic wall. In comparison with that of other mammals, the human abdominal aorta has fewer elastic laminae than would be expected based on the hemodynamic load (6). This may partly explain the propensity for aneurysms to develop in the abdominal aorta. The largely acellular adventitial layer of the aorta is composed primarily of large amounts of elastin and collagen, and it provides much of the tensile strength of the aortic wall (18, 19).

It has been suggested that failure of elastin is the initiating factor in the development of an aneurysm, resulting in an increased mechanical load on the collagen which forms a very strong but indistensible “safety net” (6, 17-19). Experimental models of aneurysm formation have shown that isolated destruction of elastin results in an arterial dilation of only 25-65 percent, and that for further aneurysmal dilation and subsequent rupture to occur there must also be failure of the collagen (6, 20).

Several factors have been proposed as contributors to the weakening of the aortic wall and aneurysmal dilation. One factor is the natural degradation of elastin. The half-life of elastin has been estimated as approximately 70 years (6), and the adult aorta does not appear to manufacture functional elastin (6, 21, 22). This may partly explain the fact that abdominal aneurysms occur primarily late in life. Some investigators have suggested that genetically determined anomalies in the constitutional proteins in the aortic wall render some individuals prone to aneurysm formation (2, 18, 23). However, as yet, no important specific genetic defects in the primary structure of the aorta have been identified.

There is a growing body of scientific evidence suggesting that an imbalance between proteolytic activity and antiproteolytic activity in the aorta is associated with the formation of abdominal aneurysms (24-32). Several studies have shown that persons with abdominal aneurysm have higher levels of elastolytic activity than persons with occlusive aortic disease or patients with neither abdominal aneurysm nor occlusive disease (25-32). The precise nature and source of the elastolytic activity is uncertain (6, 25, 29, 30). In addition to enhanced elastolytic activity, some small studies have demonstrated a reduction in the antiproteolytic activity within the aneurysm wall (27, 33, 34).

Inflammation has also been proposed as a factor weakening the aortic wall and leading to aneurysm formation. Pathologic studies have shown that abdominal aneurysms are often infiltrated by inflammatory cells involving the aortic media and adventitia (35-38). The role of and stimulus for inflammation in the formation of abdominal aneurysms has yet to be delineated. However, Gregory et al. (39) and Tilson et al. (40) have proposed a role for autoimmunity in this process.

Natural history of disease

While some abdominal aneurysms remain stable in size, the natural history of most of them involves slow expansion. Overall, most clinical case studies which have observed the natural history of these aneurysms have found that the expansion rate is variable, and some abdominal aneurysms do not appear to change appreciably in size. In most studies, the overall mean expansion rate is 0.25-0.50 cm per year (41-44). However, mean expansion rates increase as a function of size. In a surgical case series described by Guirguis and Barber (43), the expansion rate (maximal transverse diameter) was 0.2 cm per year for abdominal aneurysms in the 3- to 4-cm range and 0.4 cm per year for those in the 5- to 6-cm range. Similar findings have been reported for patients with abdominal aneurysm detected by population screening. Bengtsson et al. (45) followed 88 such patients and found that the expansion rates were quite variable. They reported mean expan-
sion rates of 0.08 cm per year among persons with abdominal aneurysms less than 4.0 cm in diameter and 0.33 cm per year among those with abdominal aneurysms with an initial diameter of 4.0 cm or more.

With increasing early detection and improved surgical prognosis, most deaths that are directly attributed to abdominal aneurysm result from aortic rupture. The risk of rupture depends on size. Although prospective data on the full natural history of abdominal aneurysm are scarce because of surgical intervention, it is estimated that the 5-year risk of rupture is approximately 75 percent for abdominal aneurysms greater than 7.0 cm in diameter (46–49). The risks of rupture for abdominal aneurysms with diameters of ≥6.0 cm and 5.0–5.9 cm have been estimated at 35 percent and 25 percent, respectively (46–49). The risk of rupture for abdominal aneurysms less than 5 cm in diameter appears to be low. In their surgical case series, Guirguis and Barber (43) reported cumulative 6-year rupture rates of 2 percent for aneurysms 4–5 cm in diameter and 1 percent for aneurysms less than 4 cm in diameter. Similar findings have been reported from other study centers (50–52).

The case fatality rate for ruptured abdominal aneurysms is extremely high. Approximately 50 percent of persons with a ruptured abdominal aneurysm who reach a hospital do not survive. Since up to 70 percent of persons with rupture do not survive long enough to reach a hospital, the overall case fatality is over 80 percent (53).

In contrast, the operative mortality for abdominal aneurysm has declined over the past two decades (53). Surgical mortality rates in the 1950s and early 1960s ranged from 13 percent to 15 percent, and they declined to 5–7 percent in the late 1960s and early 1970s (53). More recently, reported surgical mortality rates have been in the 2–5 percent range, despite an increase in surgery for persons with other comorbid conditions (53).

**METHODOLOGICAL ISSUES**

Important methodological issues must be considered in reviewing descriptive and analytic epidemiologic studies of abdominal aneurysm. Among these issues, case definition and case detection are of particular importance.

**Case definition**

There have been several proposed clinical definitions for abdominal aneurysm (16, 54–59). Most definitions use criteria that are intended to identify persons with abnormal aneurysmal dilation of the infrarenal aorta, without explicit regard to the clinical significance or prognosis. The Society for Vascular Surgery and the International Society for Cardiovascular Surgery recommend that an abdominal aneurysm be defined by an aortic diameter that is at least 50 percent greater than normal (16). However, this definition is difficult to apply, since criteria for defining "normal" aortic diameter are not clearly established and aortic diameters differ by age, sex, and body size. Zwiebel discourages specific size criteria and suggests that from a radiologic perspective, "the primary criterion for sonographic diagnosis of an aneurysm is a focal increase in the caliber of the affected vessel" (54, p. 56). However, this topographic definition may be difficult to reproduce in practice. Other researchers have proposed definitions based on the absolute or relative diameter of the infrarenal aorta. McGregor et al. (55) proposed that an abdominal aneurysm was present if the infrarenal aortic diameter was at least 3.0 cm. Although this definition may be more reproducible, such a definition does not account for the fact that the normal aortic diameter varies; therefore, definitions based on the ratio of the diameter of the infrarenal aorta relative to that of the suprarenal aorta have been developed. Sterpetti et al. (56) proposed that the infrarenal diameter exceed the suprarenal diameter by at least 1.5 times. Alcorn et al. (57) have suggested a much more sensitive case definition wherein an abdominal aneurysm is present if the infrarenal diameter exceeds the suprarenal diameter by at least 1.2 times.

The selection of a case definition that is based on clinical significance is problematic, since expansion rates are variable. Collin (58) proposed a definition based on clinical relevance wherein an abdominal aneurysm was present if the maximal diameter was 4.0 cm or the infrarenal aortic diameter exceeded the suprarenal diameter by at least 0.5 cm. The clinical rationale for using a 4.0-cm cutoff is supported by the observation that the occurrence of rupture or acute expansion is rare in smaller abdominal aneurysms (60). Another approach was proposed by Ourlie et al. (59), wherein a ratio of the aortic diameter to that of the third lumbar vertebral body that is greater than 1 is used to define a clinically significant aortic dilation. They found that this definition was better at distinguishing ruptured abdominal aneurysms (n = 36) than were definitions that used the absolute infrarenal aortic diameter, the diameter relative to the diameter of an age- and sex-matched population, or a ratio based on the diameter of the suprarenal aorta.

The choice of a case definition in epidemiologic studies of abdominal aneurysm can have a substantial impact on the results. The use of a very sensitive case definition such as that proposed by Alcorn et al. (57) results in much higher prevalence estimates than more
restrictive case definitions. Case definition may also have important implications for etiologic studies of abdominal aneurysm. The inclusion of cases defined by minimal aortic dilation may identify factors that are associated with the initiation of aneurysm formation but not factors associated with further dilation. This is an important consideration, since current concepts of abdominal aneurysm pathogenesis suggest that these processes may involve different pathophysiologic mechanisms. Factors associated primarily with degeneration of elastin in the aortic media may lead only to minor dilation (6, 20). Additional factors associated with destruction of elastin and collagen in the aortic adventitia may be required for the development of further aneurysmal dilation and aortic rupture (19).

A further difficulty in choosing a case definition for etiologic investigations of abdominal aneurysms relates to the fact that they are not pathologically homogeneous. Although the large majority are nonspecific in origin, the inclusion of cases due to familial defects in collagen or those due to causes such as trauma or infection will attenuate observed risk factor associations.

Case detection

The detection of abdominal aneurysms is hampered by the fact that they are rarely accompanied by pathognomonic symptoms. Surgical case series have demonstrated that only 19-43 percent of patients have suggestive symptoms (50, 61, 62). Clinical examination is not a highly accurate method for detection. In general clinical settings, the sensitivity of clinical examination is usually less than 50 percent (63, 64). The low sensitivity of clinical examination and the frequent lack of symptoms result in a high prevalence of undetected abdominal aneurysms (65-67). The positive predictive value of clinical examination is also low, ranging from 15 percent to 50 percent depending on the prevalence of abdominal aneurysm and the clinical criteria used (64, 68, 69).

Since many abdominal aneurysms go undetected, descriptive epidemiologic studies using data sources that rely on clinical detection are prone to underestimation of the true prevalence. In this regard, population screening studies and necropsy studies in populations with high necropsy rates are less biased. Analytic studies focusing on risk factors for abdominal aneurysm are also prone to biases due to differential case detection. Spurious associations will result when case detection is influenced by variables associated with the risk factor under study (diagnostic suspicion bias). In this regard, factors that enhance clinical scrutiny, such as the presence of coexistent conditions (particularly those involving the vascular system) or the existence of presumed risk factors, may result in spurious positive associations. This type of bias may be found in prospective studies in which case detection is not active but instead relies on routine clinical detection or death certification. Similarly, selection bias may be introduced into case-control studies unless controls are selected such that they are subject to the same level of clinical scrutiny as are the cases. Risk factor studies based on population screening are less prone to this type of bias. However, since they require a large sample size for identification of an adequate number of cases, they often rely on less precise risk factor measurement.

Temporality

The early development of an abdominal aneurysm is generally an insidious process. Therefore, most epidemiologic studies are based on prevalent cases rather than incident cases. As a result, it is difficult to determine the temporal sequence between risk factor exposure and aneurysm formation in cross-sectional and retrospective studies. Prospective studies are less prone to temporal biases. However, unless active case detection is performed at enrollment, cases prevalent at study initiation are likely to be misclassified as incident cases during the follow-up period.

Cross-sectional and retrospective studies may also be biased by the effect that some risk factors have on the natural history of abdominal aneurysm. In this regard, factors that are associated with aneurysm rupture or premature mortality may be underrepresented in case series derived cross-sectionally or retrospectively.

DESCRIPTIVE EPIDEMIOLOGY

Descriptive epidemiologic studies are generally based on prevalent cases rather than incident cases. Most early studies of the occurrence of abdominal aneurysm were based on necropsy series (11, 12, 65, 70). More recently, data from population-based clinical case series (5, 13, 71), administrative health records (1, 3, 4, 72, 73), vital statistics (3, 74, 75), and population screening programs (14, 57, 64, 76-80) have been used to describe the epidemiology of abdominal aneurysm.

Age and sex

One of the most striking and consistent findings from descriptive epidemiologic studies is the increased prevalence of abdominal aneurysm with advancing age (1, 57, 65, 70, 74, 76). Since most abdominal aneurysms are asymptomatic, it is difficult to assign and analyze the average ages of onset and incidence.
for abdominal aneurysm. Although variations in methodology and case definition make comparisons between different studies problematic, a sharp rise in prevalence has been seen in most studies after the age of 60 years (figures 1 and 2). In epidemiologic necropsy studies (65, 70) and screening studies (57, 76), prevalence is less than 1 percent among persons under 60 years of age. Thereafter, prevalence rises quickly, and it appears to plateau above 80 years of age. Accounting for this rapid increase in prevalence, the incidence of abdominal aneurysm evidently rises sharply in the sixth and seventh decades. These findings are supported by mortality data from vital statistics registers. In an analysis of US mortality data, Lilienfeld et al. (74) showed a substantial increase in the mortality rate for aortic aneurysm with age in all birth cohorts in both men and women. The sharpest increases in mortality rates were seen between the ages of 40 and 70 years, with some leveling in older age groups. A more recent review of US mortality statistics also reported higher mortality rates with advancing age, with the sharpest increase in mortality beginning between the ages of 55 and 64 years (1).

Abdominal aneurysms are substantially more common among men than among women. Studies from mortality statistics registers have consistently demonstrated a higher mortality rate among men than among women (1, 3, 4, 70, 74). Among White men and women in the United States, the male:female mortality ratio is 4.5 (74). In Canada, among persons aged ≥55 years, the male:female mortality ratio is 3.6 (3). In data from England and Wales, the age-adjusted mortality rate for aortic aneurysm was more than twice as high among men as among women (4).

Studies based on clinical cases of abdominal aneurysm have also shown a higher frequency among men. A study by Melton et al. (71) based on clinical diagnoses of abdominal aneurysm in Rochester, Minnesota, found a 2.3-fold higher crude incidence rate among men than among women between 1971 and 1980. Lilienfeld et al. (73) reviewed hospital discharge records from the Minneapolis-St. Paul, Minnesota, metropolitan area for 1979–1984. They found that age-adjusted rates of hospitalization were 5–10 times higher among men than among women. Similarly, Millar et al. (3) reported a 4.7-fold increase in the age-adjusted hospitalization rate for abdominal aneurysm among Canadian men in 1990.

Since abdominal aneurysms often escape clinical detection, studies based on death registration or clinical diagnoses may be influenced by detection bias. However, necropsy studies and screening surveys have also found a higher prevalence of abdominal aneurysm among men. In a study from Malmö, Sweden, Bengtsson et al. (70) showed that the overall prevalence of abdominal aneurysm upon necropsy was twice as high among men as among women (4.3 percent vs. 2.1 percent). The greatest difference in prevalence was for persons aged less than 80 years, after which the prevalences converged (figure 1). A
Time trends

Several studies have indicated an increase in the prevalence of abdominal aneurysm in various populations during the past few decades (3, 5, 65, 70, 71, 81). This may be partly due to an increasing size of higher risk populations. Although most studies of temporal trends have adjusted for the age distribution of the study population, there may be residual confounding due to the increasing survival of higher risk subpopulations. Another explanation for this observed increase is enhanced detection. However, several studies have also demonstrated stable or increased rates of ruptured abdominal aneurysm and emergency cases of abdominal aneurysm (5, 71, 81). Since surgical care has improved and surgery is now more common, the frequency of these cases would probably decline if increased detection of asymptomatic or uncomplicated abdominal aneurysms were not accompanied by an actual increase in incidence. Furthermore, at least one study has shown that the increase in incidence has occurred for all sizes of abdominal aneurysms. In the population-based study of clinically diagnosed abdominal aneurysms in Rochester, Minnesota, Melton et al. (71) demonstrated that while the largest age-adjusted increase in the prevalence was for small and asymptomatic abdominal aneurysms, there was also a 16 percent increase in the incidence of large abdominal aneurysms between 1960–1961 and 1971–1980.

In Western Australia between 1980–1982 and 1986–1988, age-standardized mortality due to abdominal aneurysm increased by 36 percent among men over age 55 and by 24 percent among women over age 55 (5). The largest increases in mortality were observed for deaths occurring during emergency and elective hospital admissions, with smaller increases for necropsy study conducted in Kansas City, Missouri, by McFarlane (65) revealed a 2.6-fold increase in prevalence for persons aged less than 70 years and a 1.6-fold increase in persons over the age of 70. Most screening surveys have included only men. However, a recent screening survey in Rotterdam, The Netherlands, found a much higher prevalence among men than among women (76). Overall, the prevalence was almost 6 times higher among men. The male:female prevalence ratio was quite consistent in all age groups over 55 years (figure 2). Similarly, a recent screening study of US veterans by Lederle et al. (80) found that males had a 1.6- to 4.5-fold higher prevalence than females, depending on the case definition used. The screening study by Alcorn et al. (57) found a prevalence ratio of 2.3 for men versus women (14.2 percent vs. 6.2 percent) in persons aged 65 years or older.
nonhospital deaths. In Göteborg, Sweden, the age-standardized mortality rate for ruptured abdominal aneurysm increased by an average of 2.4 percent per year between 1960 and 1980, despite a decline in surgical mortality for ruptured aneurysm (81). In interpreting these findings, the possible influence of increased detection of small abdominal aneurysms on the attribution of mortality to abdominal aneurysm should be considered.

In Canada, mortality statistics demonstrate a stable age-adjusted mortality rate for ruptured and unruptured abdominal aneurysms between 1979 and 1991 (3). In contrast, the age-adjusted hospitalization rate increased by 52 percent among men and 29 percent among women over the same time period (3).

Necropsy studies from Sweden and the United States have shown substantial increases in the necropsy detection rate over the past few decades among both men and women (65, 70). Bengtsson et al. (70) reported that the age-standardized prevalence of abdominal aneurysm at necropsy increased by an average of 4.7 percent per year among men and by 3.0 percent per year among women between 1958 and 1986 in Malmö, Sweden. McFarlane (65) also reported an increase in the prevalence of abdominal aneurysm between 1950–1959 and 1970–1984 in Kansas City among both men (1.5-fold increase) and women (2.5-fold increase). Although the authors of these reports did not note any temporal changes in the necropsy techniques or case definitions over time, the extent to which such changes occurred would have influenced the observed temporal increases in prevalence.

Racial differences

There are indications of racial differences in the prevalence of abdominal aneurysm and abdominal aneurysm-specific mortality, especially among men (1, 82, 83). US mortality statistics show that the White:Black age-adjusted mortality ratios for abdominal aneurysm are 2–3 among men (1). In contrast, among US women, the White:Black mortality ratios are close to 1. A case-control study by LaMorte et al. (82) based on hospital discharge records in Massachusetts found that the odds ratio for abdominal aneurysm repair was 2.4 for White race. Racial differences observed in these studies may be influenced by higher detection rates among Whites. A study in North Carolina reported on the prevalence of abdominal aneurysm discovered incidentally upon necropsy or abdominal computed tomographic scan (83). Among persons over 50 years of age, the highest prevalence was seen among White men (5.4 percent), followed by White women (1.9 percent) and Black men and women (1.0 percent and 1.1 percent), respectively.

While this study is less likely to have been biased by differential clinical detection, the age distribution of patients was not reported, so confounding due to age cannot be excluded as an explanation. The screening study by Lederle et al. (80) reported odds ratios of 1.4–2.4 for White race compared with Black race after adjustment for multiple variables.

Etiologic implications of descriptive epidemiology

Descriptive studies using differing methodologies have revealed some important themes that must be considered in assessing the etiology of abdominal aneurysm.

Age effects. The incidence of abdominal aneurysm increases with age. With regard to extrinsic risk factors for abdominal aneurysm, the sharp increase with age might indicate some combination of the following circumstances: 1) the exposure to the risk factor must be prolonged, 2) there is a long latency period between risk factor exposure and aneurysm development, and 3) the aorta becomes more susceptible to risk factors with advancing age.

Sex differences. Men are at higher risk for abdominal aneurysm than women. The reasons for this are not clear. Hormonal factors, genetic susceptibility, increased exposure to important risk factors, or a combination of these variables may play a role among men.

Temporal trends. In many populations, the prevalence of abdominal aneurysm appears to be rising. This trend contrasts with declining rates of clinical manifestations of atherosclerosis, such as coronary heart disease and stroke, and appears to indicate differences in etiologic factors (71, 84–86). However, these contrasting temporal trends may also indicate a longer latency between risk factor exposure and disease development for abdominal aneurysm.

Racial differences. Although racial differences in the occurrence of abdominal aneurysm have not been extensively studied, it appears that in the United States abdominal aneurysms are substantially more common among White men than among Black men. Differences between White women and Black women are small. Much of this difference among men could be due to differential detection resulting from enhanced access to clinical care in the White population. Possible etiologic explanations include differential genetic susceptibility between men and women and increased exposure to important risk factors among White men. The incidence of common clinical manifestations of atherosclerosis (such as coronary heart disease) does not show such striking differences between Black men and White men in the United States (84, 87); thus, from an etiologic perspective, the difference is inconsistent.
with the theory that abdominal aneurysms are a manifestation of atherosclerosis.

**RISK FACTOR STUDIES**

Until recently, there were very few analytic studies directed toward identifying risk factors for abdominal aneurysm. So far, most studies have focused only on atherosclerotic risk factors (see table 1).

**Cigarette smoking**

Tobacco smoking is one of the most commonly cited risk factors for abdominal aneurysm. It has been assessed in several analytic epidemiologic studies of varying designs (table 1). Five prospective studies have demonstrated a strong association between tobacco smoking and aortic aneurysm, with relative risks ranging from 2.6 to 9.0 for various levels of regular smoking (88–92). In three studies, a significant dose response was demonstrated (88–90), while the other two studies only reported on one measure of tobacco exposure (91, 92).

There were potentially important methodological problems in all of these prospective studies. Three of the studies included thoracic aortic aneurysms, which may have different risk factors than abdominal aneurysms (88–90). All of the studies relied primarily on passive methods of case detection, rendering them susceptible to detection bias. Four of the studies relied on death certification (88–91), and only one of these verified the death certificate diagnosis (88). The prospective study by Reed et al. (92) relied primarily on review of hospital and clinical records; thus, for the most part, only clinically apparent abdominal aneurysms were included. Adjustment for risk factors

<table>
<thead>
<tr>
<th>Author(s) and location of study (ref. no.)</th>
<th>Case definition and detection</th>
<th>Statistical association with abdominal aortic aneurysm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reed et al., United States (92)</td>
<td>Clinical (82%) and autopsy (18%) AAAs</td>
<td>Positive, positive (systolic BP*, not diastolic BP)</td>
</tr>
<tr>
<td>Hammond and Garfinkel, United States (89)</td>
<td>Death certificate (all aortic aneurysms)</td>
<td>Positive, NA</td>
</tr>
<tr>
<td>Strachan, United Kingdom (91)</td>
<td>Death certificate (AAA)</td>
<td>Positive, positive (diastolic BP, not systolic BP)</td>
</tr>
<tr>
<td>Doll and Peto, United Kingdom (90)</td>
<td>Death certificate (nonsyphilitic aortic aneurysms)</td>
<td>Positive, NA</td>
</tr>
<tr>
<td>Kahn, United States (88)</td>
<td>Death certificate (nonsyphilitic aortic aneurysms)</td>
<td>Positive, NA</td>
</tr>
<tr>
<td>Collin et al., United Kingdom (77)</td>
<td>Ultrasound; diameter ≥ 4.0 cm or suprarenal/infrarenal difference ≥ 0.5 cm</td>
<td>NA, positive (clinical diagnosis)</td>
</tr>
<tr>
<td>Pleumeekers et al., The Netherlands (76)</td>
<td>Ultrasound; diameter ≥ 3.5 cm or suprarenal/infrarenal ratio &gt; 1.5</td>
<td>Positive, positive (clinical hypertension)</td>
</tr>
<tr>
<td>Alcorn et al., United States (57)</td>
<td>Ultrasound; diameter ≥ 3.0 cm or suprarenal/infrarenal ratio ≥ 1.2</td>
<td>Positive, positive (clinical hypertension)</td>
</tr>
<tr>
<td>Lederle et al., United States (80)</td>
<td>Ultrasound; diameter ≥ 3.0 cm or suprarenal/infrarenal ratio ≥ 1.5</td>
<td>Positive, positive (clinical hypertension)</td>
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**Cross-sectional (screening) studies**

<table>
<thead>
<tr>
<th>Author(s) and location of study (ref. no.)</th>
<th>Case definition and detection</th>
<th>Statistical association with abdominal aortic aneurysm</th>
</tr>
</thead>
<tbody>
<tr>
<td>LaMorte et al., United States (82)</td>
<td>Surgical AAA cases</td>
<td>Positive, positive (clinical hypertension)</td>
</tr>
<tr>
<td>Cole et al., Canada (93)</td>
<td>Hospital-based AAA cases</td>
<td>Positive, positive (clinical hypertension)</td>
</tr>
<tr>
<td>Norrgård et al., Sweden (100)</td>
<td>Surgical AAA cases</td>
<td>NA, positive (VLDL* + LDL* cholesterol, HDL cholesterol)</td>
</tr>
</tbody>
</table>

* BP, blood pressure; NA, data not available; HDL, high density lipoprotein; VLDL, very low density lipoprotein; LDL, low density lipoprotein.
other than age was performed in only two of the studies (91, 92).

Cross-sectional ultrasound screening surveys and case-control studies have also demonstrated an association between cigarette smoking and abdominal aneurysm (57, 76, 78–80, 82, 93). The reported exposure measurement in each of these studies was either current smoking or past smoking history, without further exploration of a dose response. Odds ratio estimates from the cross-sectional studies have generally been lower than those reported from prospective or case-control studies. This may be partly explained by the fact that studies based on screening surveys are less prone to detection bias. Another reason for these differences may be the use of a more sensitive and less specific case definition for abdominal aneurysm in screening studies. In support of this notion, two of the screening studies found stronger associations when more stringent case definitions were used (78, 80).

Family history

Familial aggregation of abdominal aneurysm has been demonstrated in several studies using various designs (94–99). In a large case-control study by Darling et al. (94), 15 percent of abdominal aneurysm patients reported an abdominal aneurysm in at least one first degree relative as compared with 1.8 percent of controls (odds ratio = 9.7). A similar study by Johansen and Koepsell (95) reported that 19 percent of the cases had at least one first degree relative with an abdominal aneurysm in comparison with only 2.4 percent of controls (odds ratio = 11.6).

Other studies have estimated the prevalence of abdominal aneurysm among family members of abdominal aneurysm patients without comparison with an explicit control group. In these studies, 11–20 percent of cases were found to have at least one first degree relative with an abdominal aneurysm. Some of these studies relied solely on the report of the index case (96, 97). A potential bias inherent in this approach is the influence a positive family history of abdominal aneurysm may have on the clinical detection of an abdominal aneurysm in other family members. Another potential source of bias in these studies is differential recall, with the diagnosis of an abdominal aneurysm leading to enhanced knowledge or recall of one’s family history.

Other studies have been based on ultrasound screening of family members (98, 99). Although this will reduce detection bias, interpretation of these results is complicated by a lack of information on whether there was familial clustering of other risk factors, notably smoking. For example, in a screening study by Webster et al. (99), all of the family members who were discovered to have an abdominal aneurysm were smokers. Similarly, in a study by Fitzgerald et al. (98), 73 percent of the newly discovered familial cases were in smokers.

Increased blood pressure

Increased blood pressure is a commonly cited risk factor for abdominal aneurysm. However, the results of analytic studies which have assessed the association between increased blood pressure and abdominal aneurysm have been mixed (57, 76–80, 82, 91–93). The results of prospective and case-control studies have generally indicated that increased blood pressure is associated with abdominal aneurysm (82, 91–93). However, screening studies, which are less prone to detection bias, have generally not found this association (76, 77) or have found a weak association (57, 80).

Two prospective studies found an increase in the risk of abdominal aneurysm with increasing blood pressure (91, 92). Reed et al. (92) reported that increasing systolic blood pressure at baseline was associated with an increased risk of subsequent clinically diagnosed abdominal aneurysm. The relative risk for persons in the fourth quartile of systolic blood pressure (>145 mmHg) was 2.0 in comparison with persons with systolic blood pressures less than 119 mmHg at baseline. Results of the Whitehall Study, reported by Strachan (91), showed that each 10-mmHg increase in diastolic blood pressure at baseline was associated with a relative risk of 1.5 for subsequent mortality due to abdominal aneurysm. As was discussed above, the widespread medical opinion that hypertension is a risk factor for abdominal aneurysm may have influenced these results through detection bias. Furthermore, since increased blood pressure has been reported to increase the expansion rate and risk of rupture, some of the observed increase in risk may be a measure of influence on the development of complications related to abdominal aneurysm (i.e., rupture or acute expansion) rather than on the actual incidence of abdominal aneurysm (51).

Two case-control studies have also assessed the association between elevated blood pressure and abdominal aneurysm (82, 93). A hospital-based study by LaMorte et al. (82) compared histories of hypertension, as documented in the hospital charts, between 102 patients who underwent surgical repair of an abdominal aneurysm and controls who had an appendectomy at the same two hospitals. They found an odds ratio of 3.6 for clinically diagnosed hypertension, after adjustment for age, sex, smoking, and race. Cole et al. (93) compared hospital-based abdominal aneurysm cases with a hospital control group comprised of persons with conditions other than cardiovas-
cular disease, diabetes, or cancer. They found that the prevalence of hypertension (defined as blood pressure \(\geq 140/90\) or current treatment for elevated blood pressure) was 47 percent among abdominal aneurysm cases and 27 percent among controls.

Results from screening studies in which detection bias has been reduced have not consistently demonstrated an increased prevalence of elevated blood pressure among persons with abdominal aneurysm (76, 77, 79). A screening study by Plemmekeers et al. (76) found that the age-adjusted prevalence of hypertension, defined as systolic blood pressure \(>160\) mmHg or diastolic blood pressure \(>95\) mmHg or current antihypertensive treatment, was higher among abdominal aneurysm patients than among those without abdominal aneurysm (29 percent vs. 27 percent among men; 42 percent vs. 33 percent among women). However, these differences were not statistically significant. Results from the Oxford Screening Programme of men aged 65–74 years, reported by Collin et al. (77), also failed to show an increased incidence of hypertension (diastolic blood pressure \(>105\) mmHg or current use of antihypertensive medication) among those with an abdominal aneurysm. Two screening studies have indicated an association between hypertension and abdominal aneurysm. Alcorn et al. (57) found that current treatment of hypertension was associated with a slightly increased prevalence of abdominal aneurysm (10.4 percent vs. 8.7 percent; \(p = 0.042\)). However, they found no association between average levels of systolic or diastolic blood pressure and abdominal aneurysm. Lederle et al. (80) also found that hypertension was associated with a small but statistically significant association between a self-reported history of hypertension and abdominal aneurysm (adjusted odds ratios were 1.14–1.25 for various aneurysm case definitions).

**Serum lipids and lipoproteins**

Several studies have examined the relation between serum levels of lipids and lipoproteins and abdominal aneurysm (57, 76, 80, 91–93, 100). Two prospective studies have produced conflicting results (91, 92). Reed et al. (92) found that the incidence of clinically diagnosed abdominal aneurysm increased with increasing baseline serum levels of cholesterol but not with levels of triglycerides. Overall, the relative risk was 2.3 when persons in the fourth quartile of serum cholesterol level (\(>240\) mg/dl) were compared with those in the first quartile (<193 mg/dl). In contrast, the study by Strachan (91) found no association between baseline cholesterol level and risk of death due to abdominal aneurysm. In both of these studies, relative risk estimates were adjusted for age, sex, blood pressure, and smoking.

In two case-control studies, investigators have examined the relation between abdominal aneurysm and serum levels of cholesterol and lipoproteins (93, 100). Norrgård et al. (100) compared serum levels of total cholesterol, high density lipoprotein (HDL) cholesterol, very low density lipoprotein (VLDL) plus low density lipoprotein (LDL) cholesterol, and triglycerides among 51 surgical abdominal aneurysm cases to levels in a population-based control group. Persons with a history of cardiovascular, liver, or endocrine disease were excluded from the control group. Significantly increased levels of triglycerides and VLDL + LDL cholesterol and significantly decreased levels of HDL cholesterol were found among men and women with abdominal aneurysm in comparison with controls (100). There was no significant difference in serum levels of total cholesterol. A study by Cole et al. (93) compared serum levels of HDL cholesterol among 78 hospital-based abdominal aneurysm cases and controls appearing at the same hospital for conditions other than cardiovascular disease, diabetes, or cancer. They found that cases had significantly decreased HDL cholesterol levels compared with controls. In both of these case-control studies, the exclusion of controls with diseases associated with altered levels of serum lipids and lipoproteins, but not cases with such diseases, may have exacerbated selection biases and spuriously increased the association between cholesterol and lipoprotein abnormalities and abdominal aneurysm.

Cross-sectional screening studies have also provided conflicting results. The study by Plemmekeers et al. (76) found a small but statistically significant increase in mean serum total cholesterol levels among men with abdominal aneurysm. An increase was also seen among women with abdominal aneurysm, but it was not statistically significant. No differences in serum levels of HDL cholesterol were reported between persons with and without abdominal aneurysm in either men or women. In contrast, the study by Alcorn et al. (57) found a significantly increased prevalence of abdominal aneurysm among those with lower HDL cholesterol levels (<40 mg/dl). They also found that persons with LDL cholesterol levels greater than 160 mg/dl had a slightly higher prevalence of abdominal aneurysm than those with lower levels. Lederle et al. (80) found statistically significant adjusted odds ratios of 1.33–1.54 (depending on the case definition) for self-reported high cholesterol levels. However, they reported that there were missing data on hypercholesterolemia for many of the subjects. Furthermore, when they compared self-reports with clinical findings for a subset of the participants, they found that the accuracy of the self-reports was suboptimal.

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Diabetes mellitus

The few previous analytic studies regarding diabetes mellitus and abdominal aneurysm suggest that there is either no association or an inverse association. Two prospective studies found no association between serum glucose levels and subsequent abdominal aneurysm (91, 92). A case-control study in Massachusetts by LaMorte et al. (82) found that the prevalence of diabetes among persons who underwent surgery for abdominal aneurysm was slightly lower than that among patients who had appendectomy and substantially lower than that among patients who had femoral bypass. Assessment of the presence of diabetes was based on chart reviews or computerized hospital records.

Screening studies have also shown a low prevalence of diabetes among persons with abdominal aneurysm (57, 79). Smith et al. (79) found that persons with an abdominal aneurysm detected by a community screening program had a lower prevalence of diabetes (5 percent) than persons without abdominal aneurysm (6 percent). The Rotterdam Study also found a lower prevalence of diabetes among persons with abdominal aneurysm (76). Alcorn et al. (57) found little difference in the prevalence of abdominal aneurysm by blood glucose level. Lederle et al. (80) found a significant inverse association between diabetes and abdominal aneurysm after adjusting for multiple factors.

Other risk factors

Several other risk factors have been proposed for abdominal aneurysm (101–103). One study of 47 abdominal aneurysm patients reported a higher frequency of a deficient phenotype of α-1-antitrypsin than would be expected in the general population (103). Two studies have found a much higher prevalence of inguinal hernia among men with abdominal aneurysm than among patients with aortic occlusive disease, prompting the authors to suggest that there may be an enhanced, generalized proteolytic process among abdominal aneurysm patients (101, 102). A few studies have examined the relation between abdominal aneurysm and trace metals such as copper and zinc; results have been inconsistent (24). Recently, case series described by Juvonen et al. (104) and Blasi et al. (105) have provided evidence that Chlamydia pneumoniae infection is common in abdominal aneurysm tissue. The study by Blasi et al. (105) also showed that a high proportion of abdominal aneurysm patients had serologic evidence of past C. pneumoniae infection. However, since neither of these studies included a non-aneurysm control group, it is difficult to interpret the etiologic significance of their findings.

Etiologic implications of risk factor studies

Previous research into risk factors for abdominal aneurysm has provided some important clues regarding etiology, but many questions remain unanswered.

Cigarette smoking. The relation between smoking and abdominal aneurysm seems indisputable, since several analytic studies using a variety of methods have found a strong epidemiologic association (57, 76, 78–80, 82, 88–93). While the strength of the association and the presence of a dose response suggest a causal relation, etiologic mechanisms are unclear. It may be that some of smoking's effect is mediated through atherosclerosis. However, since most persons with aortic atherosclerosis do not develop aneurysms, other mechanisms are probably also present. Enhanced elastolysis is one possibility. Cigarette smoking has been shown to perturb the protease/antiprotease imbalance, leading to degradation of elastic tissue in the lungs (106–108). Such a process may also affect the aorta.

Hypertension. On the basis of previous epidemiologic studies, the relation between elevated blood pressure and abdominal aneurysm is not entirely clear. Because there is some evidence that beta blockers may reduce the expansion rate of abdominal aneurysms (109, 110), these studies may have been partly confounded by the use of antihypertensive agents in hypertensive subjects. If hypertension does play a role in abdominal aneurysm formation, it may do so through an increase in the hemodynamic load on the aortic wall. In support of this, there is some evidence that elevated blood pressure increases the expansion rate of existing abdominal aneurysms (51).

Lipids and lipoproteins. The relation between abdominal aneurysm and serum levels of lipids and lipoproteins is also unclear. In general, studies that have found positive associations have relied on clinically detected cases. Three screening studies using different methods with respect to case definition and exposure measurement have provided conflicting results. To the extent that serum lipids and lipoproteins are implicated in the causation of abdominal aneurysm, their effect may be mediated through their atherogenic properties.

Diabetes mellitus. The few studies that have examined the association between diabetes mellitus and abdominal aneurysm have demonstrated either no relation or an inverse relation. This finding appears to conflict with the atherosclerotic theory of abdominal aneurysm pathogenesis. It has been suggested that diabetes causes a macroangiopathy that is separate from its atherogenic effects and is characterized by a loss of compliance and calcification of the aorta (111–114). These changes may stabilize the aorta and render it somewhat resistant to aneurysmal dilatation.
Family history. The observation of a familial tendency for abdominal aneurysm suggests a role for genetic factors in the etiology of abdominal aneurysm. However, the genetic basis of abdominal aneurysm remains unclear. Research directed toward identification of genetic defects in genes coding for matrix proteins, connective tissue proteases, and antiproteases has not yielded definitive results. Recently, some investigators have also proposed a role for genetically determined autoimmune mechanisms in abdominal aneurysm pathogenesis (38, 40).

CONCLUSIONS

Despite its increasing public health importance, abdominal aneurysm remains an enigmatic disease. However, recent research has brought new insight into its pathophysiology. Discoveries with respect to abdominal aneurysm risk factors and etiologic mechanisms could have important public health benefits. First, identification of modifiable risk factors provides an opportunity for primary prevention in high risk populations. Second, since abdominal aneurysm is a slowly progressive disease, understanding its pathophysiology offers the hope of therapeutic intervention that can alter the natural history of disease and improve outcomes. In this regard, it will be important to distinguish risk factors for dilation and rupture from those associated with the initiation of abdominal aneurysm formation. Third, elucidation of factors that are associated with the risk of developing an abdominal aneurysm would facilitate the identification of high risk individuals. This may offer the hope of secondary prevention of abdominal aneurysm complications should the benefits of screening be demonstrated in clinical trials.

The atherosclerotic theory of abdominal aneurysm causation appears to be overly simplistic in light of emerging evidence from epidemiologic and basic research studies. Still, more conclusive research is required to clarify the relation between atherosclerotic risk factors and abdominal aneurysm. In particular, the associations between hypertension and serum lipids and lipoproteins and abdominal aneurysm require more investigation. The relation between diabetes mellitus and abdominal aneurysm also merits further research. If the initial findings of an inverse relation are verified, new insight may be gained with respect to aortic biology and pathophysiology. Because of the methodological difficulties involved in studying abdominal aneurysm, the generation of more definitive findings in these areas might require the use of a large prospective study which features active case detection with periodic radiologic imaging.

Analytic epidemiologic studies will also be required in order to explore emerging etiologic hypotheses. Genetic epidemiologic approaches should be rigorously applied to better understand the genetic basis of abdominal aneurysm. There have been many small clinical studies and case series exploring factors such as proteolytic and antiproteolytic activity, autoimmunity, and infection in relation to abdominal aneurysm. However, to begin to test these hypotheses, larger, well designed epidemiologic studies with better measurement and analysis of other risk factors will be required.

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