SECTION 5

GENITOURINARY SYSTEM CANCERS

A summary of epidemiologic studies of red meat or processed meat intake and prostate cancer, kidney cancer, bladder cancer, and testicular and penile cancers.

PROSTATE CANCER

Cancer that forms in the tissues of the prostate, which is a walnut-sized reproductive gland in men located below the bladder, is referred to as prostate cancer. This gland contains cells that produce seminal fluid, which helps transport semen. Prostate cancer is the most commonly diagnosed malignancy in U.S. men, accounting for approximately one-quarter of all male cancers. This malignancy is responsible for approximately 10% of all cancer deaths among U.S. men. Worldwide, this disease is the second most common cancer in men, with only lung cancer accounting for more cancer diagnoses per year (Parkin et al. 2005).

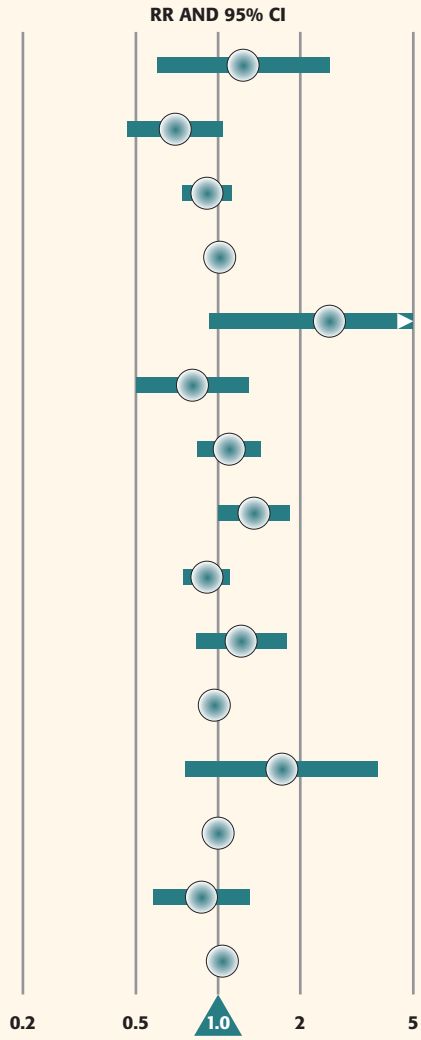
Epidemiologic studies have identified some important risk factors for prostate cancer; however, the etiology is largely unknown. The risk of prostate cancer increases with increasing age, particularly after age 65. African-American men are more likely to be diagnosed than Caucasian men (Ries et al. 2007; ACS 2008). Persons with a positive family history of prostate cancer in a first-degree relative may be more likely to develop this malignancy.

The relationships between behavioral and dietary factors and prostate cancer have been examined in numerous epidemiologic studies; however, the role of these factors in potentially increasing or decreasing the risk of prostate cancer has not been clearly defined. In the 2007 WCRF/AICR report on diet and cancer, it was concluded that foods containing lycopene or selenium, and supplementation with selenium probably decrease the risk of prostate cancer, and that diets high in calcium probably increase the risk. In the same report, the association between processed meat intake and prostate cancer was judged to be suggestive, although it was acknowledged that data were limited.

More than a dozen cohort studies evaluated red meat consumption and prostate cancer, and results from these studies are not indicative of an increased risk of this malignancy (Alexander et al. 2009). In a 2007 analysis of approximately 300,000 men, Cross et al. (2007) reported no association (RR = 1.01, 95% CI: 0.96-1.07) with prostate cancer among men in the

FIGURE 5.1
PROSPECTIVE STUDIES OF RED MEAT INTAKE AND PROSTATE CANCER

AUTHOR AND YEAR	COHORT
Allen 2004	Hiroshima, Nagasaki-Japan Cohort Study
Chan 2000	Alpha-Tocopherol Beta-Carotene Cancer Prevention Study
Cross 2005	PLCO Cancer Screening Trial
Cross 2007	NIH-AARP Diet and Health Study
Gann 1994	Physicians Health Study
Hsing 1990	Lutheran Brotherhood Cohort Study
Koutros 2008	Agricultural Health Study
Le Marchand 1994	Hawaii Cohort Study
Michaud 2001	Health Professionals Follow-Up Study
Mills 1989	Seventh Day Adventist Cohort Study
Park 2007	Multiethnic Cohort Study
Rodriquez 2006 (African-Americans)	Cancer Prevention Study II
Rodriquez 2006 (Caucasians)	Cancer Prevention Study II
Rohrmann 2007	CLUE II
Schuurman 1999	Netherlands Cohort Study



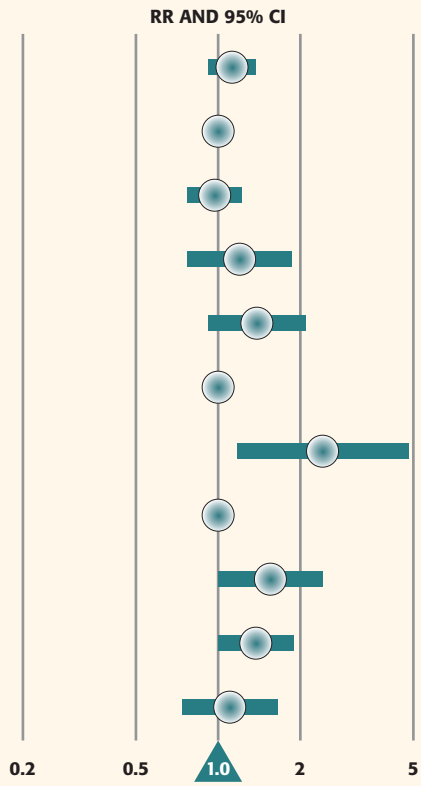
highest category of red meat intake. In a smaller sub-group analysis of this cohort, several correlates (e.g., cooking practices, heme iron, nitrates, dietary mutagens) of meat intake were examined (Sinha et al. 2009). No associations between intake of pan-fried, microwaved, or broiled meat and prostate cancer were reported but a significant positive association was observed for grilled/barbequed meat (Sinha et al. 2009). In addition, no significant associations were observed for any of the heterocyclic amines that were evaluated or for meat doneness. Weakly elevated significant associations between nitrite and nitrate intake and advanced prostate cancer were reported, and no associations were observed for total dietary iron but a slightly elevated, albeit significant, association was found for heme iron (Sinha et al. 2009).

Rodriguez et al. (2006) evaluated meat intake and prostate cancer in the American Cancer Society's (ACS) Cancer Prevention Study II (CPS II) Nutrition Cohort. A total of 5,028 and 85 incident prostate cancer cases were identified among 64,897 Caucasian men and 693 African-American men in the cohort, respectively. No association for the highest intake of red meat was found among Caucasian men (RR = 1.0, 95% CI: 0.9-1.1) and a non-significant positive association was observed among African-American men (RR = 1.7, 95% CI: 0.8-3.9), although data were considerably more sparse among African-American men.

In an analysis of data from the Agricultural Health Study, Koutros et al. (2008) reported no significant associations between consumption of red meat, beef steaks, hamburgers, pork chops/ham steaks, or bacon/sausages and total or advanced prostate cancer.

FIGURE 5.2
PROSPECTIVE STUDIES OF PROCESSED MEAT INTAKE AND PROSTATE CANCER

AUTHOR AND YEAR	COHORT
Cross 2005	PLCO Cancer Screening Trial
Cross 2007	NIH-AARP Diet and Health Study
Koutros 2008	Agricultural Health Study
Le Marchand 1994	Hawaii Cohort Study
Michaud 2001 (metastatic)	Health Professionals Follow-Up Study
Park 2007	Multiethnic Cohort Study
Rodriquez 2006 (African-Americans)	Cancer Prevention Study II
Rodriquez 2006 (Caucasians)	Cancer Prevention Study II
Rohrmann 2007	CLUE II
Schuurman 1999	Netherlands Cohort Study
Severson 1989	Hawaii Cohort Study



Results from case-control studies of red meat consumption and prostate cancer are variable; while some associations have been positive, some have been null and inverse. No association for red meat was found in a recently published Canadian case-control study of 1,800 prostate cancer cases (OR for highest intake category = 1.0, 95% CI: 0.8-1.3) (Hu et al. 2008).

Results for processed meat from the cohort studies are more heterogeneous than for red meat, and relatively more positive associations have been reported. However, null associations have been observed in the three largest cohort investigations (Cross et al. 2007; Park et al. 2007; Rodriquez et al. 2006). As with red meat intake, case-control studies of processed meat intake and prostate cancer have produced highly variable results. In the aforementioned Canadian case-control study (Hu et al. 2008), a statistically significant positive association between the highest intake category of processed meat and prostate cancer was reported (OR = 1.6, 95% CI: 1.2-2.2).

In a 2008 publication of the European Prospective Investigation into Cancer and Nutrition (EPIC) study, Crowe et al. (2008) evaluated the relationship between dietary fat intake, including fat from red and processed meat sources, and prostate cancer among approximately 150,000 men. The authors reported decreased risks of total (RR = 0.95, 95% CI: 0.83-1.07), low-grade (RR = 0.97, 95% CI: 0.79-1.18), and high-grade (RR = 0.84, 95% CI: 0.64-1.10) prostate cancer for each per-unit increase in fat from red and processed meat sources.

The available epidemiologic evidence is not supportive of an independent association between consumption of red meat and prostate cancer, as findings from the largest and most well conducted prospective cohort studies have been null. Regarding processed meat, the majority of studies have indicated an increased risk of prostate cancer. However, findings across studies have been variable and associations in some of the largest cohort studies have not been supportive of an independent relation between processed meat intake and prostate cancer (Alexander et al. 2009).

KIDNEY CANCER

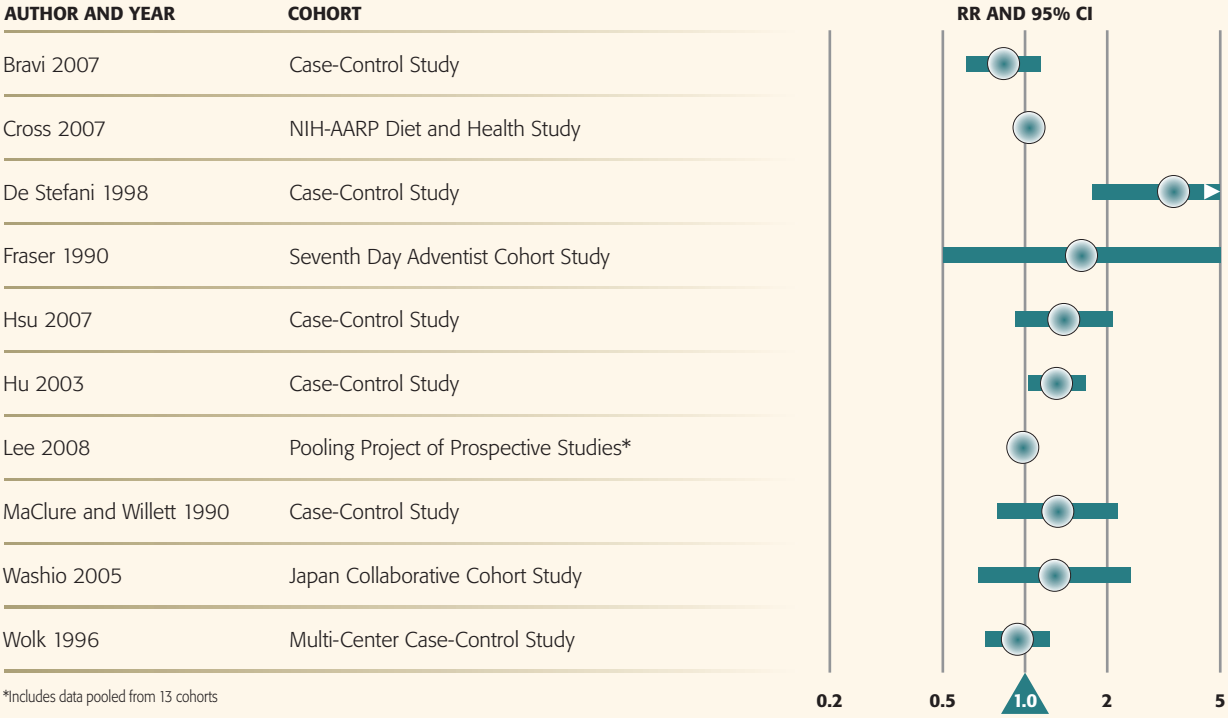
The kidneys are the organs responsible for filtering waste products from the blood. Cancer that forms in the tissues of the kidney is referred to as kidney cancer or renal cancer. Cancers of the kidney and renal pelvis (referred to as kidney cancer henceforth) are the seventh most common cancers among U.S. men and the ninth most common cancers among U.S. women (Jemal et al. 2008). Kidney cancer accounts for approximately 3.8% of all new cancer cases and 2.3% of all cancer deaths among U.S. men and women (Jemal et al. 2008). In the United States and Europe, this malignancy is almost twice as common in men as women and the average age at the time of diagnosis is in the early 60s (McLaughlin et al. 2006; Parkin et al. 2002). An increasing trend in incidence and mortality rates have been observed for kidney cancer over the past 30 years, with the largest increases found among African-American men and African-American women (Ries et al. 2008).

Epidemiologic investigations have identified some important risk factors for kidney cancer. Cigarette smoking and obesity have been established as causal factors for increasing the risk of kidney cancer; each of these factors may be responsible for 20% to 30% of all new cases (McLaughlin et al. 2006; Lindblad et al. 2002; Calle and Kaaks 2004).

In 1997, WCRF/AICR concluded that red meat consumption is a possible cause of kidney cancer; however, in their 2007 report they judged that the available epidemiologic evidence was limited-suggestive and no conclusions were drawn. Faramawi et al. published a meta-analysis in the same year (2007), and the authors concluded that red meat and processed meat were positively associated with kidney cancer risk. Their analysis, however, was based on data from only six case-control studies of red meat and four case-control studies of processed meat.

In a recent publication of red meat and processed meat based on an evaluation of the Pooling Project of Prospective Studies of Diet and Cancer, Lee et al. (2008) analyzed primary data for 530,469 women and 244,483 men from 13 international cohorts for which 1,478 kidney cancer cases were observed. Lee and colleagues found no association between the highest level of red meat consumption and kidney cancer, and they observed a weakly elevated non-significant association for processed meat intake. Moreover, no trend ($p = 0.93$) of kidney cancer risk based on increasing red meat intake categories was reported, and no association for each increase of two

FIGURE 5.3
PROSPECTIVE AND CASE-CONTROL STUDIES OF RED MEAT INTAKE AND KIDNEY CANCER



*Includes data pooled from 13 cohorts

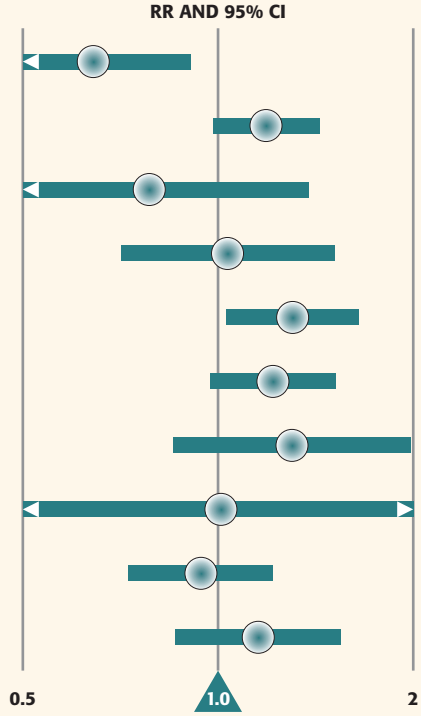
servings of red meat per week (RR = 1.00, 95% CI: 0.95-1.06) was observed. The authors reported a 1% increased risk of kidney cancer for every two-serving increase of processed meat consumption per week, but this association was not statistically significant.

Alexander and Cushing (2009) conducted a comprehensive quantitative assessment evaluating the association between red meat and processed meat intake and kidney cancer, based on all available epidemiologic data. Specifically, data reported in the Pooling Project publication were combined with data from independent cohort and case-control studies using a meta-analysis design. The summary association for all studies that reported results for red meat was 1.12 (95% CI: 0.98-1.29; p-value for heterogeneity = 0.015), and the summary association based on data from prospective cohorts was 1.02 (95% CI: 0.91-1.15). Five studies were identified that simultaneously adjusted for smoking, body mass index, and total energy intake. The summary association based on the analysis of these studies was 1.02 (95% CI: 0.91-1.15). No significant association was observed in the meta-analysis of processed meat consumption (summary relative risk = 1.07, 95% CI: 0.94-1.23), although a significant association was observed when only data from cohort studies were analyzed (summary relative risk = 1.19, 95% CI: 1.03-1.37). As with red meat, the summary association was attenuated among the five studies that controlled for the potential confounding influence of smoking, body mass index, and total energy intake (summary relative risk = 1.05, 95% CI: 0.86-1.29).

Epidemiologic studies have elucidated some key factors responsible for increasing the risk of kidney carcinogenesis; however, consumption of meat is not one of the accountable factors. Collectively, results from epidemiologic cohort and case-control studies of red meat and processed meat are inconsistent, while many associations are in the positive direction, several studies observed decreased risks of kidney cancer. Although the summary associations based on the meta-analysis were positive, all were weak in magnitude, most were not statistically significant, and associations were close to the null value among studies that adjusted for smoking, body mass index, and total energy intake (Alexander and Cushing 2009). Furthermore, no consistent patterns or trends of increased risks with increasing levels of red or processed meat intake are reported in the individual studies. In summary, the epidemiologic evidence, based on a substantial number of studies, is not supportive of an independent relationship between red meat or processed meat consumption and kidney cancer.

FIGURE 5.4
PROSPECTIVE AND CASE-CONTROL STUDIES OF PROCESSED MEAT INTAKE AND KIDNEY CANCER

AUTHOR AND YEAR	COHORT
Bravi 2007	Case-Control Study
Cross 2007	NIH-AARP Diet and Health Study
De Stefani 1998	Case-Control Study
Hsu 2007	Case-Control Study
Hu 2003	Case-Control Study
Lee 2008	Pooling Project of Prospective Studies*
MaClure and Willett 1990	Case-Control Study
Washio 2005	Japan Collaborative Cohort Study
Wolk 1996	Multi-Center Case-Control Study
Yuan 1998	Case-Control Study



*Includes data pooled from 13 cohorts

BLADDER CANCER

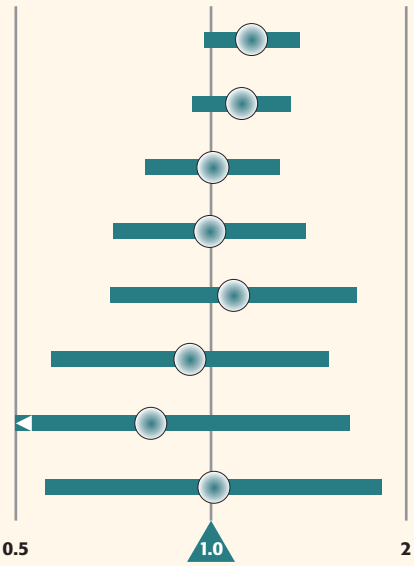
The bladder is a hollow organ that is responsible for storing urine, which it receives from the kidney through tubes called ureters. The bladder is composed of several cellular layers, and most bladder cancers are transitional cell carcinomas, which begin in cells of the inner lining of the bladder. Bladder cancer is more common among men than women, and more frequently diagnosed among Caucasians than African-Americans (Jemal et al. 2008). Smoking is perhaps the most well-established risk factor for bladder cancer, and persons who smoke have an approximate two-fold risk of developing this malignancy. Because dietary carcinogens may be excreted through the urine, this cancer site seems to be a viable candidate for the attribution of foods or food compounds in the development of malignancy. Despite this, epidemiologic studies have not revealed any dietary factors responsible for increasing the risk of bladder cancer.

Some key cohort studies have evaluated the relationship between meat consumption and bladder cancer. In a 2009 publication of a Swedish cohort study of women, Larsson et al. observed no associations between red meat or processed meat intake and bladder cancer. The authors concluded that their results do not support the hypothesis that red/processed meat is associated with developing bladder cancer. In a U.S. cohort, Cross et al. (2007) reported weakly elevated but non-significant associations between red and processed meat intake and cancer of the bladder. In addition, the authors observed no significant trends of increased risk with increased levels of consumption. In a combined analysis of the Health Professionals Follow-Up Study (HPFS) and the Nurses' Health Study (NHS), non-significant inverse associations were reported for red meat, hamburger, and hot dogs, no association was reported for processed meat, and a statistically significant positive association was observed for the highest intake level of bacon (Michaud et al. 2006).

FIGURE 5.5
RECENT PROSPECTIVE STUDIES OF RED AND PROCESSED MEAT INTAKE AND BLADDER CANCER

AUTHOR AND YEAR	COHORT
Cross 2007 (Processed Meat)	NIH-AARP Diet and Health Study
Cross 2007 (Red Meat)	NIH-AARP Diet and Health Study
Larsson 2008 (Processed Meat)	Swedish Mammography Cohort Study
Larsson 2008 (Red Meat)	Swedish Mammography Cohort Study
Michaud 2006 (Processed Meat) (M)	Health Professionals Follow-Up Study
Michaud 2006 (Red Meat) (M)	Health Professionals Follow-Up Study
Michaud 2006 (Processed Meat) (W)	Nurses' Health Study
Michaud 2006 (Red Meat) (W)	Nurses' Health Study

M: men; W: women



Associations from case-control studies have been somewhat inconsistent. A marginally significant 30% increased risk was reported for red meat and a significant 60% increased risk was reported for processed meat in a Canadian case-control study (Hu et al. 2008). Tavani et al. (2000) observed a significant 60% increased risk among the highest consumers of red meat in a study conducted in Italy. In contrast, Wakai et al. (2004) observed non-significant decreased risks for beef, pork, ham and sausage, and Castelao et al. (2004) reported non-significant inverse associations for the highest intake levels of processed meat and preformed nitrosamine. In a recently published case-control study conducted in Spain, a non-significant odds ratio of 0.8 was reported for red meat intake and a non-significant odds ratio of 1.2 was reported for processed meat intake (Garcia-Closas et al. 2007).

Cancer cell

Some large prospective cohort studies and several case-control studies of red meat and processed meat intake and bladder cancer have been published, facilitating a comprehensive assessment of the epidemiologic literature. Results from cohort studies have been generally null, with non-significant associations at or near 1.0, and some relative risks in the positive and inverse directions. Findings from case-control studies have been more variable, with positive as well as inverse associations being reported. In summary, the available epidemiologic evidence does not support an independent association between intake of red meat or processed meat and the development of bladder cancer.

Results from cohort studies have been generally null, with non-significant associations at or near 1.0, and some relative risks in the positive and inverse directions.

TESTICULAR AND PENILE CANCERS

The testicles (i.e., testes), are male reproductive glands that produce sperm and the hormone testosterone. Young and middle-aged men are at greatest risk for developing testicular cancer, although this malignancy is rare. The primary risk factor for testicular cancer is a condition called cryptorchidism, or undescended testes. Penile cancer, although very rare in the United States and Europe, is more common in certain locations of South America and Africa (ACS 2008). Circumcision shortly after birth can decrease the risk of developing penile cancer, while HIV infection or infection with the human papillomavirus (HPV) may increase risk.

No dietary factors have been established as contributing to the risk of testicular or penile cancer. In a recent case-control study conducted in Canada, Hu et al. (2008) reported that the highest consumers of processed meat had a statistically significant 50% increased risk of testicular cancer. Red meat was not associated with cancer of the testes in this study. In summary, the available epidemiologic data are limited regarding testicular and penile cancer, and the scientific community has not implicated meat consumption as being involved in the development of these malignancies.