# Chapter 6
# Cancer


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**Table 6.3*S*  Case-control studies on smoking and primary liver cancer**

| Study | Design/population | Findings (95% CI)[a] | Comments |
|---|---|---|---|
| Trichopoulos et al. 1980 | • 79 cases<br>• 204 controls<br>• 1976–1977<br>• Greece | • Ever smoker: 5.5 (2.0–15.6) among HBV negatives<br>• Cigarettes/day (within 5 years of diagnosis):<br>– 1–10: 1.3<br>– 11–20: 2.5[b]<br>– 21–30: 3.7[b]<br>– ≥31: 8.4[b] | Association confined to persons who were HBV negative; effect persisted after adjusting for alcohol consumption |
| Lam et al. 1982 | • 106 cases<br>• 107 controls<br>• 1977–1980<br>• Hong Kong, China | • Ever smoker: 1.3 (0.7–2.4)<br>– 1–19 cigarettes/day: 1.0 (0.5–10.7)<br>– ≥20 cigarettes/day: 1.5 (0.8–2.8)<br>• HBsAg positive: 0.3 (0.1–1.4)<br>• HBsAg negative: 2.9 (0.8–10.7) | Association confined to persons who were HBV negative and had the heaviest smoking exposure |
| Stemhagen et al. 1983 | • 265 cases<br>• 530 controls<br>• 1975–1980<br>• United States | • Ever smoker, men: 0.7 (0.5–1.1)<br>• Ever smoker, women: 1.0 (0.6–1.7) | Adjusted for age; no difference when adjusted for alcohol consumption ; no dose-response association |
| Yu et al. 1983 | • 78 cases<br>• 78 controls<br>• 1975–1979<br>• United States | • Current smokers compared with never and long-term former smokers:<br>– ≤20 cigarettes/day: 1.2 (0.6–2.5)<br>– >20 cigarettes/day: 2.6 (1.0–6.7)<br>– Former smokers: 1.1 (0.3–4.0) | In stratified analyses, significant risk observed only among those with both heavy smoking (>20 cigarettes/day) and heaviest consumption of alcohol (>80 g/day) |
| Hardell et al. 1984 | • 83 cases (men who died of primary liver cancer or liver cancer not designated as primary or secondary)<br>• 200 controls<br>• 1974–1981<br>• Sweden | • Current and former smokers: 1.1 (CI not reported) | Small association disappeared after controlling for alcohol consumption |
| Filippazzo et al. 1985 | • 120 HCC cases<br>• 360 controls (hospitalized patients with cirrhosis, other tumors, or with diagnoses other than those 2)<br>• 1980–1984<br>• Italy | • Current smoker: 0.9 (CI not reported)<br>• HCC compared with noncirrhosis, noncancer controls: 0.8 (0.4–1.5) | Compared HCC cases with 3 control groups; estimates are unadjusted |
| Kew et al. 1985 | • 240 cases<br>• 240 hospital controls<br>• South Africa | • <1.0 for any smoking and also for ≥20 cigarettes/day (CI not reported)<br>• Among HBV negatives, OR = 1.25 for ever smokers | Controls matched for age, race, gender, recruitment site, and urban/rural background |
| Austin et al. 1986 | • 86 cases<br>• 161 hospitalized controls<br>• United States | • Ever smoker: 1.1 (0.5–2.4)<br>• Current smoker: 1.6 (0.7–3.7)<br>• Cigarettes/day among current smokers:<br>– <20: 1.7<br>– ≥20: 1.2 | Controls matched for age, gender, race, and residence; adjusted for consumption of alcohol; HBsAg negative only |

**Table 6.3*S* Continued**

| Study | Design/population | Findings (95% CI)[a] | Comments |
|---|---|---|---|
| Trichopoulos et al. 1987 | • 194 cases<br>• 456 hospitalized controls<br>• 1976–1984<br>• Greece | • ≥30 cigarettes/day: 7.3<br>• HBV negative: 2.8<br>• HBV positive: 1.3 | Association confined to persons who were HBV negative |
| La Vecchia et al. 1988 | • 151 cases<br>• 1,051 hospitalized controls<br>• 1984–1987<br>• Italy | • Former smoker: 0.6 (0.4–1.0)<br>• Current smoker: 0.9 (0.6–1.5) | Adjusted for age, gender, geographic area, hepatitis, cirrhosis, and consumption of alcohol; no dose-response relationship for cigarette smoking |
| Lu et al. 1988 | • 131 cases<br>• 207 controls<br>• 1985<br>• Taiwan | • Ever smoker:<br>– Unadjusted OR = 1.1 (0.7–1.8)<br>– Adjusted OR = 1.33 for smokers<br>– $\chi 2$ for trend = 0.88 (p >0.05) | Adjusted for gender and HBsAg status; in multivariate analysis, smoking behaviors (duration in years, and number of cigarettes smoked/day) were not associated with HCC |
| Yu et al. 1988 | • 165 cases<br>• 465 controls<br>• 1969–1985<br>• United States | • 3.3; p <0.05 | Association limited to current-smoking females >50 years of age |
| Ferraroni et al. 1989 | • 151 cases<br>• 1,944 controls<br>• 1983–1988<br>• Italy | • Former smoker: 0.9<br>• Cigarettes/day (findings not significant):<br>– <15: 0.9<br>– 15–24: 0.7<br>– ≥25: 0.8 | Adjusted for age, gender, consumption of alcohol, education level, marital status, and coffee consumption |
| Hiyama et al. 1990 | • 299 cases<br>• 266 controls<br>• 1984–1987<br>• Japan | • Pack-years:<br>– <20: 1.0 (baseline)<br>– 20–39: 1.9 (1.1–3.3)<br>– 40–59: 2.0 (1.1–3.6)<br>– ≥60: 1.0 (0.5–1.9) | Adjusted for HBsAg status, age, gender, consumption of alcohol, and family history of liver cancer |
| Kew et al. 1990 | • 46 cases<br>• 92 controls<br>• Africa | • Ever smoker: 2.2 (0.8–6.1) | Adjusted for age and geography; included only Black females |
| Mayans et al. 1990 | • 96 cases<br>• 190 controls<br>• 1986–1988<br>• Spain | • Cigarettes/day:<br>– 1–20: 1.4<br>– >20: 1.1 | No association based on unadjusted data or after adjusting for HBV or consumption of alcohol |
| Olubuyide and Bamgboye 1990 | • 100 cases<br>• 100 controls<br>• 1987–1988<br>• Nigeria | • Ever smoker:<br>– All: 1.7 (0.9–3.1)<br>– Men: 1.5 (0.8–2.8)<br>– Women: 7.1 (0.7–26.5) | Unadjusted |

**Table 6.3*S* Continued**

| Study | Design/population | Findings (95% CI)[a] | Comments |
|---|---|---|---|
| Tsukuma et al. 1990 | • 229 cases<br>• 266 controls<br>• 1983–1987<br>• Japan | • Former smoker: 0.7 (0.3–1.9)<br>• Current smoker: 2.5 (1.4–4.5)<br>• Cigarette index (lifetime number of cigarettes):<br>– 0–399: Reference<br>– 400–799: 1.7 (1.0–2.8)<br>– 800–1,199: 1.8 (1.0–3.1)<br>– >1,200: 1.0 (0.5–1.8) | Adjusted for age and gender; index adjusted for HBsAg, history of transfusion, and family history |
| Chen et al. 1991 | • 200 cases<br>• 200 controls<br>• 1985–1987<br>• Taiwan | • Cigarettes/day—crude OR [AOR]:<br>– 1–10: 1.1 (0.6–2.0) [1.05]<br>– 11–20: 1.9 (1.2–3.1) [1.48]<br>– ≥21: 3.0 (1.5–5.8) [2.62] | Adjusted for consumption of alcohol, HBsAg/HBeAg status, family history of HCC, gender, age, ethnic group, and residence at time of cancer |
| Choi and Kahyo 1991 | • 216 cases<br>• 648 controls<br>• 1986–1990<br>• Republic of Korea | • Former smoker: 0.6 (0.4–1.2)<br>• Current smoker: 1.0 (0.7–1.6)<br>• Cigarettes/day:<br>– 1–20: 1.2 (0.8–1.8)<br>– 21–40: 0.6 (0.3–1.2)<br>– ≥41: 0.5 (0.1–2.6)<br>• Duration (years):<br>– 1–19: 0.7 (0.4–1.3)<br>– 20–39: 1.0 (0.6–1.6)<br>– ≥40: 1.9 (0.4–1.8) | Adjusted for age, marital status, education level, consumption of alcohol, and HBV status |
| Lin et al. 1991 | • 200 cases (HBV-negative males without alcoholic cirrhosis in an aflatoxin-endemic region of China)<br>• 200 controls<br>• 1984–1986<br>• China | • Ever smoker: 0.6 (0.4–1.0) | Included only men because smoking among females was rare |
| Srivantanakul et al. 1991 | • 65 cases<br>• 65 controls<br>• Thailand | • Current smokers compared with never and occasional smokers: 1.0 (0.4–2.4)<br>• HBV negative: 1.8 (0.5–5.9) | Unadjusted estimates; smoking not included in multivariate models |
| Tzonou et al. 1991 | • 185 cases<br>• 432 controls<br>• 1976–1984<br>• Greece | • HCC cases with cirrhosis: 2.3 (0.9–5.9)<br>• HCC cases without cirrhosis: 2.1 (1.1–4.0)<br>• HBsAg-positive cases and controls: 1.7 (0.5–5.6)<br>• HBsAg-negative cases and controls: 2.4 (1.2–4.7) | Adjusted for age, gender, and HBsAg/HCV status |
| Yu et al. 1991 | • 74 cases<br>• 162 controls<br>• 1984–1990<br>• United States | • Unadjusted:<br>– Former smoker: 1.6 (0.7–3.5)<br>– Current smoker: 2.5 (1.2–5.0)<br>• Adjusted for consumption of alcohol:<br>– Former smoker: 1.1 (0.4–2.6)<br>– Current smoker: 2.1 (1.1–4.3) | |

**Table 6.3*S* Continued**

| Study | Design/population | Findings (95% CI)[a] | Comments |
|---|---|---|---|
| Yu et al. 1991 | • 127 cases<br>• 127 controls<br>• 1986–1987<br>• Taiwan | • Cigarettes/day (matched OR):<br>– 1–10: 1.1 (0.5–2.2)<br>– 11–20: 1.8 (1.0–3.4)<br>– >20: 1.7 (0.7–4.5)<br>• Cigarettes/day (adjusted for HBV, HCV, consumption of alcohol, and peanut consumption):<br>– 1–10: 0.4 (0.1–1.9)<br>– 11–20: 1.3 (0.4–4.2)<br>– >20: 2.1 (0.3–13.5) | Matched OR; adjusted for HBV, HCV, consumption of alcohol, and peanut consumption |
| Mohamed et al. 1992 | • 101 cases<br>• 101 controls<br>• South Africa | • Cigarettes/day:<br>– 0–19, Men: 2.2 (0.3–6.3)<br>– 0–19, Women: 1.3 (0.5–3.4)<br>– ≥20, Women: 0.7 (0.2–2.5) | Adjusted for consumption of alcohol, age, and HBV status |
| Ross et al. 1992 | • 22 cases<br>• 140 controls<br>• 1986–1989<br>• China | • Ever smoker: 1.8 (0.6–5.6) | Adjusted for age, education level, residence, aflatoxin exposure, consumption of alcohol, and HBsAg; males only |
| Tanaka et al. 1992 | • 204 cases<br>• 410 controls<br>• 1985–1989<br>• Japan | • Current smokers: 1.5 (0.8–2.7)<br>• Former smokers: 1.5 (0.8–2.8) | Adjusted for age, gender, consumption of alcohol, HBsAg status, history of blood transfusion, and family history of liver disease; there was no significant trend in risk with years smoked |
| Peters et al. 1994 | • 86 cases<br>• 86 controls<br>• 1986–1993<br>• Germany | • Current smoker with >40 pack-years: 1.2 (0.5–2.9) | Adjusted for consumption of alcohol and HBV/ HCV status |
| Pyong et al. 1994 | • 90 cases<br>• 249 controls<br>• 1989–1992<br>• Japan | • Males only, cigarettes/day:<br>– 1–20: 0.7 (0.2–2.4)<br>– >20: 0.4 (0.1–1.6) | Adjusted for age, gender, HBV/HCV status, history of blood transfusion, and consumption of alcohol |
| Goritsas et al. 1995 | • 51 cases<br>• 85 controls<br>• 1989–1992<br>• Greece | • Ever smoker: 1.6 (0.9–2.0) | Adjusted for age, gender, alcohol abuse, HBV/HCV status; HBsAg by smoking interaction; no HCV by smoking interaction |
| Siemiatycki et al. 1995 | • 48 cases<br>• 2,238 controls (had cancer at sites not previously associated with cigarette smoking)<br>• 1979–1986<br>• Canada | • Ever smoker: 0.9 (0.4–2.1)<br>• Pack-years:<br>– <25: 1.4 (0.5–3.8)<br>– 25–49: 0.7 (0.3–1.9)<br>– 50–74: 0.7 (0.2–2.2)<br>– ≥75: 0.8 (0.3–2.7) | Adjusted for age; men, 35–70 years of age only |

**Table 6.3*S* Continued**

| Study | Design/population | Findings (95% CI)[a] | Comments |
|---|---|---|---|
| Tanaka et al. 1995 | • 120 cases<br>• 257 controls<br>• 1983–1989<br>• Japan | • Current smoker: 1.8 (0.9–3.4)<br>• Former smoker: 2.8 (1.1–6.9)<br>• Ever smoker, male: 1.9 (1.2–2.8)<br>• Pack-years:<br>– 0.1–12.9: 2.4 (1.1–4.9)<br>– ≥13.0: 1.8 (0.8–3.7) | Adjusted for age, study category (except for ever smokers), HBV status, history of blood transfusion, family history of liver cancer, and consumption of alcohol; combined analysis of 3 studies; partial overlap with Tanaka et al. (1992) |
| Shin et al. 1996 | • 203 cases<br>• 406 controls<br>• 1990–1993<br>• Republic of Korea | • Current smoker, moderate level: 2.3 (0.4–11.7)<br>• Current smoker, high level (>20 cigarettes/day for >10 years): 1.1 (0.3–2.5) | Adjusted for HBV/HCV status, history of *Clonorchis sinensis*, history of hepatitis, other liver disease, consumption of alcohol, and SES |
| Mukaiya et al. 1998 | • 104 cases<br>• 104 controls<br>• 1991–1993<br>• Japan | • ≥5 pack-years vs. <5 pack-years: 3.3 (1.3–8.3)<br>• ≥10 pack-years vs. <10 pack-years: 3.3 (1.3–8.3) | |
| Koide et al. 2000 | • 84 cases<br>• 84 controls<br>• 1994<br>• Japan | • Ever smoker: 5.4 (1.1–27) | Adjusted for age, gender, HBV/HCV infection, and *CYP2E1* genotype |
| Kuper et al. 2000 | • 333 cases<br>• 360 controls<br>• 1995–1998<br>• Greece | • <40 cigarettes/day:<br>– Former smoker: 1.2 (0.7–1.9)<br>– Current smoker: 1.5 (0.7–3.0)<br>– Ever smoker: 1.6 (0.8–2.9)<br>• ≥40 cigarettes/day:<br>– Former smoker: 1.2 (0.8–1.9)<br>– Current smoker: 1.6 (0.9–2.9)<br>– Ever smoker: 2.5 (1.1–5.5) | Adjusted for age, gender, education level, HBV, and HCV |
| Takeshita et al. 2000 | • 85 cases<br>• 125 controls<br>• 1993–1996<br>• Japan | • Current smokers: 1.6 (0.7–3.5)<br>• Former smokers: 0.7 (0.3–1.5) | Adjusted for age and consumption of alcohol; males only |
| Lam et al. 2001 | • 27,507 cases<br>• 13,054 controls<br>• 1998<br>• Hong Kong, China | • Ever smoker, men:<br>– 35–69 years of age: 1.6 (1.3–1.9)<br>– ≥70 years of age: 1.2 (0.9–1.5)<br>• Ever smoker, women:<br>– 35–69 years of age: 1.4 (0.8–2.4)<br>– ≥70 years of age: 1.4 (0.9–2.0) | Adjusted for age and education level |
| Hassan et al. 2002 | • 115 cases<br>• 230 hospital-based controls with cancer of skin and GI, urogenital, and respiratory tracts<br>• 1984–1985<br>• United States | • Current smoker: 1.2 (0.6–2.4) | Controls were matched on age, gender, and recruitment date; adjusted for diabetes, consumption of alcohol, HBV, and HCV |

**Table 6.3*S* Continued**

| Study | Design/population | Findings (95% CI)[a] | Comments |
|---|---|---|---|
| Yu et al. 2002 | • 248 cases<br>• 248 controls<br>• 1995–1997<br>• China | • Ever smokers: 0.7 (0.3–1.7) | Adjusted for age, gender, residence, and HBV infection |
| Chen et al. 2003 | • 36,000 cases (liver cancer deaths)<br>• 17,000 controls (deaths due to liver cirrhosis)<br>• 1986–1988<br>• China | • Men:<br>– Ever smoker: 1.4 (1.3–1.4)<br>– 10 cigarettes/day: 1.3<br>– 20 cigarettes/day: 1.5<br>– 30 cigarettes/day: 1.6<br>• Women:<br>– Ever smoker: 1.2 (1.1–1.3)<br>– <20 cigarettes/day: 1.1<br>– ≥20 cigarettes/day: 1.5 | Controls were indirectly controlled for HBV infection and consumption of alcohol; adjusted for age and locality; RR independent of age, urban/rural status, or age at start of smoking |
| Farker et al 2003 | • 70 cases<br>• 87 controls<br>• Germany | • Former smoker: 2.5 (1.2–5.0)<br>• Current smoker: 2.4 (0.9–6.4) | Unadjusted estimates |
| Matsuo 2003 | • 222 cases<br>• 222 controls<br>• 1995–2000<br>• Japan | • Cumulative cigarette smoking (pack-years):<br>– Male: 1.05 (0.82–1.36)<br>– Female: 1.80 (0.40–8.14) | Adjusted for history of blood transfusion, consumption of alcohol, and diabetes |
| Munaka et al. 2003 | • 78 cases<br>• 138 controls<br>• 1997–1998<br>• Japan | • Ever smoker: 1.2 (0.6–2.7) | Adjusted for age and gender |
| Shimada et al. 2003 | • 53 cases<br>• 80 controls<br>• 2001<br>• Japan | • Smoking index (lifetime number of cigarettes): 1.2 (0.8–1.9) | Controlled for consumption of alcohol and HBV infection |
| Yuan et al 2004 | • 295 cases<br>• 435 controls (population-based in; included never smokers and recent ex-smokers)<br>• 1984–2002<br>• Los Angeles County, California | • Current or recent exsmokers compared with never smokers or long-term exsmokers: 1.6 (1.1–2.2)<br>• Cigarettes/day:<br>– 1–20: 1.5 (1.0–2.5)<br>– >20: 1.6 (1.1–2.4)<br>• HBV negative and HCV negative: 1.7 (1.0–3.0) | Exsmokers defined as those who quit within the last 10 years; adjusted for age, gender, race, education level, consumption of alcohol, and diabetes; no clear interaction between smoking and consumption of alcohol, diabetes, or HBV/HCV |
| Gelatti et al. 2005 | • 200 cases<br>• 400 controls<br>• 1999–2002<br>• Italy | • Pack-years:<br>– <20: 0.9 (0.5–1.7)<br>– ≥20: 0.7 (0.4–1.2) | Adjusted for HBV, HCV, and consumption of alcohol |

**Table 6.3*S* Continued**

| Study | Design/population | Findings (95% CI)[a] | Comments |
|---|---|---|---|
| Marrero et al. 2005 | • 70 cases<br>• 140 controls (included non-liver disease outpatients and people with cirrhosis)<br>• 2002–2004<br>• United States | • Smoking status (compared with healthy controls):<br>– Current smokers: 10.9 (3.5–34.0)<br>– Ever smokers: 12.3 (4.4–34.2)<br>– Former smokers: 13.3 (4.5–38.9)<br>• Pack-years (compared with healthy controls):<br>– <20: 1.2 (0.7–1.5)<br>– ≥20: 63.7 (17–144)<br>• Pack-years (compared with cirrhotic controls):<br>– <20: 0.7 (0.4–1.2)<br>– ≥20: 4.9 (2.2–10.6) | Not adjusted for current, ever, or former smoking effects; estimates for pack-years adjusted for race, obesity, consumption of alcohol, and HBV/HCV |
| Franceschi et al. 2006 | • 229 cases<br>• 431 controls<br>• 1999–2002<br>• Italy | • Current smokers: 1.1 (0.6–2.2)<br>– 1–14 cigarettes/day: 1.2 (0.6–2.4)<br>– ≥15 cigarettes/day: 1.1 (0.5–2.5)<br>• HBsAg positive or anti-HCV positive: 44.3 (19.7–99.3)<br>• HBsAg negative and anti-HCV negative: 1.0 (0.5–2.0)<br>• Former smokers: 0.8 (0.4–1.5) | Adjusted for age, gender, education level, HBV and HCV infections; when stratified by HBV/HCV infection, no association of smoking and HCC among those who were negative, strong association among positive |
| Zhu et al. 2007 | • 168 cases<br>• 1,910 controls<br>• 1984–1988<br>• United States | • Former smokers: 1.9 (1.1–3.3)<br>• Current smokers: 1.5 (0.8–2.7)<br>• Packs/day (OR):<br>– <1: 1.4 (0.7–2.7)<br>– 1–2: 1.7 (0.9–3.0)<br>– >2: 1.8 (0.9–3.8)<br>– p trend = 0.068 | Adjusted for demographics, SES, consumption of alcohol, and detailed medical history; risk estimates similar but less precise for HCC only; males only |
| Hara et al. 2008 | • 209 cases<br>• 256 hospital controls and 381 chronic liver disease controls<br>• 2001–2004<br>• Japan | • Hospital controls:<br>– Former smokers: 0.8 (0.3–2.3)<br>– Current smokers: 1.8 (0.6–5.1)<br>• Chronic liver disease controls:<br>– Former smokers: 1.0 (0.6–1.7)<br>– Current smokers: 2.5 (1.4–4.6) | Adjusted for age, gender, HBV, HCV, and consumption of alcohol; no dose-response association with intensity or pack-years of smoking; recent heavy exposure appeared to be associated most with risk among patients with chronic liver disease |

**Table 6.3*S* Continued**

| Study | Design/population | Findings (95% CI)[a] | Comments |
|---|---|---|---|
| Hassan et al 2008 | • 319 cases<br>• 1,061 controls (spouses/ family members of non-HCC cancer patients)<br>• 2000–2006<br>• United States | • Ever smokers, both genders: 1.5 (1.0–2.1)<br>• Ever smokers, men: 1.9 (1.2–3.1)<br>– HCV positive: 136.3 (43.2–429.0)<br>– HCV negative: 1.8 (1.1–2.9)<br>– HBsAg1 positive or anti-HBc13 positive: 9.6 (3.9–22.4)<br>– HBsAg1 negative and anti-HBc13 negative: 2.0 (1.2–3.3)<br>• Ever smokers, women: 1.1 (0.5–1.8)<br>– HCV negative: 1.2 (0.6–2.0)<br>– HBsAg1 positive or anti-HBc13 positive: 6.7 (1.9–24.1)<br>– HBsAg1 negative and anti-HBc13 negative: 1.1 (0.6–1.9)<br>• Former smokers, all: 1.4 (0.9–2.1)<br>• Former smokers, men:<br>– Quit <10 years: 2.4 (1.2–4.9)<br>– Quit ≥10 years: 1.7 (0.9–2.8) | Adjusted for age, race, education level, marital status, state of residency, HCV, HBV, diabetes, heavy consumption of alcohol, and family history of cancer; significant risk (without dose-response relationship) also observed for intensity, duration, and pack-years of smoking for men, nonsignificant for women; protective associations tended to be observed for noncigarette tobacco use and for passive exposure to smoke |
| Hassan et al 2009 | • 420 cases<br>• 1,104 controls<br>• 2000–2008<br>• United States | • Ever smoker (OR): 1.8 (1.3–2.4)<br>– ≤20 pack-years (OR): 1.4 (0.9–2.1)<br>– >20 pack-years (OR) = 2.0 (1.4–2.9) | Extension of study by Hassan and colleagues (2008); adjusted for age, gender, race, education level, HBV, HCV, consumption of alcohol, diabetes, and family history of liver cancer |
| Jeng et al. 2009 | • 200 cases<br>• 200 controls<br>• 2003–2004<br>• Taiwan | • Ever smoker, unadjusted: 2.3 (1.5–3.5)<br>• Compared with nonsmokers who were negative for viral hepatitis:<br>– Smokers without viral hepatitis had an increased risk for HCC: 44.4 (17.8–116)<br>– Smokers with viral hepatitis had an increased risk for HCC: 90 (32.1–266) | Performed interaction analysis of smoking and viral hepatitis (HBsAg or anti-HCV); adjusted for age and gender |
| Soliman et al. 2010 | • 150 cases<br>• 150 controls<br>• 2007–2009<br>• Egypt | • Ever smoker: 1.4 (0.7–2.8):<br>– Moderate use: 1.8 (0.8–4.5)<br>– Heavy use: 1.7 (0.8–3.7) | Adjusted for age, gender, and HBV/HCV status |
| Wan et al. 2011 | • Asian immigrant patients with chronic HBV infection who were recruited from a single hospital site<br>• 44 early-onset and 124 late-onset cases<br>• 432 early-onset and 199 late-onset controls<br>• 2003–2009<br>• United States | • Early onset of HCC among ever smokers: 3.4 (1.5–8.0)<br>• No significant association between smoking and late onset of HCC in adjusted model | Early onset defined as males <40 years of age and females <50 years of age; adjusted for gender, cirrhosis, and family history of HCC |

**Table 6.3*S* Continued**

| Study | Design/population | Findings (95% CI)[a] | Comments |
|---|---|---|---|
| Ha et al. 2012 | • Hospital-based case-control study<br>• 259 cases<br>• 781 controls (having chronic liver disease)<br>• 2001–2009<br>• United States | • Lifetime tobacco use >11,000 packs: 1.7 (1.0–2.9) | Adjusted for race, age, gender, cirrhosis, level of alpha-fetoprotein, consumption of alcohol, diabetes, and etiology of liver disease (including HBV and HCV) |
| Polesel et al. 2012 | • 185 cases<br>• 412 controls<br>• 1999–2002<br>• Italy | • Current smoker: 1.5 (0.8–2.7) | Adjusted for location, gender, age, birthplace, education level, HCV, HBV, heavy consumption of alcohol, diabetes, and obesity |

*Notes:* **AOR** = adjusted odds ratio; **CI** = confidence interval; **g** = gram; **GI** = gastrointestinal; **HBc13** = hepatitis B core antibody; **HBeAG** = hepatitis B e antigen; **HBsAg** = hepatitis B surface antigen; **HBV** = hepatitis B virus; **HCC** = hepatocellular carcinoma; **HCV** = hepatitis C virus; **OR** = odds ratio; **pack-years** = the number of years of smoking multiplied by the number of packs of cigarettes smoked per day; **RR** = relative risk; **SES** = socioeconomic status.
[a]Findings are reported as RRs in comparisons with never smokers unless indicated otherwise.
[b]Results significantly higher than 1.00.

**Table 6.4*S* Cohort studies on smoking and primary liver cancer**

| Study | Design/population | Findings (95% CI)[a] | Comments |
|---|---|---|---|
| Basa et al. 1977 | • 16,492 followed<br>• 754 cases<br>• 1968–1973<br>• Philippines | • Ever smoker:<br>– Men 1.5 (p = 0.01)<br>– Women 2.6 (p = 0.001)<br>• Current smoker:<br>– Men: 1.3<br>– Women: 1.9 (p = 0.01) | Adjusted for age |
| Oshima et al. 1984 | • Nested case-control study among HBsAg-positive blood donors<br>• 9,646 followed<br>• 20 cases<br>• 1972–1980<br>• Japan | • Men, cigarettes/day:<br>– >30: 5.8 (1.0–34.2)<br>– ≤30: 1.7 (0.4–6.4) | |
| Tu et al. 1985 | • HBV-positive cohort<br>• 12,222 followed (all men)<br>• 70 cases<br>• 1980–1982<br>• China | • HBV carrier, mortality rate:<br>– Nonsmoker: 332.8<br>– Current smoker: 737.9<br>– ≤19 cigarettes/day: 660.1<br>– ≥20 cigarettes/day: 1,519 (p <0.05)<br>• HBV noncarrier, mortality rate:<br>– Nonsmoker: 115.1<br>– Current smoker: 99.9<br>– ≤19 cigarettes/day: 96.3<br>– ≥20 cigarettes/day: 145.2 | Adjusted for age and consumption of alcohol |
| Shibata et al. 1986 | • Nested case-control study of male fishermen and farmers<br>• 1,316 followed<br>• 22 cases<br>• Japan | • 1–19 cigarettes/day: 2.0 (0.4–9.8)<br>• ≥20 cigarettes/day: 1.8 (0.4–8.9) | Adjusted for consumption of alcohol |
| Carstensen et al. 1987 | • 25,129 followed (all men)<br>• 54 cases<br>• 1963–1979<br>• Sweden | • Former smoker: 1.7<br>• Current smoker: 3.0<br>• Cigarettes/day:<br>– 1–7: 1.6<br>– 8–15: 3.3<br>– >15: 4.1 | Relative death rates standardized for age and residence; $\chi^2$ test for trend of cigarettes/day reported as significant |
| Kono et al. 1987 | • Male physician subjects<br>• 5,130 followed<br>• 51 cases<br>• 1965–1983<br>• Japan | • Ever smokers compared with never and occasional smokers:<br>– 1–19 cigarettes/day: 1.1 (0.6–2.2)<br>– ≥20 cigarettes/day: 1.0 (0.5–2.2)<br>• Current and past smokers compared with never and occasional smokers:<br>– 1–19 cigarettes/day: 1.1 (0.6–2.2)<br>– ≥20 cigarettes/day: 1.0 (0.5–2.2) | Adjusted for age and consumption of alcohol |
| Hirayami 1989 | • 265,118 followed (all men)<br>• 123 cases<br>• 1966–1982<br>• Japan | • Current smoker: 3.1 (1.8–5.4)<br>• Cigarettes/day:<br>– 1–29: 3.1 (1.8–5.4)<br>– ≥30: 6.8 (3.6–13.1) | |

**Table 6.4*S* Continued**

| Study | Design/population | Findings (95% CI)[a] | Comments |
|---|---|---|---|
| Hiyama et al. 1990 | • 13,171 followed (all men)<br>• 93 cases<br>• 1969–1985<br>• Japan | • Ratio of observed/expected: 1.4 (1.1–1.7) | |
| Hiyama et al. 1990 | • Nested case-control study<br>• 8,646 followed (all men)<br>• 22 cases<br>• 1972–1992<br>• Japan | • 10–29 cigarettes/day:<br>– Crude OR: 1.7 (0.4–6.4)<br>– Adjusted OR: 1.2<br>• ≥30 cigarettes/day:<br>– Crude OR: 5.8 (1–34.2)<br>– Adjusted OR: 6.3 | Controls matched by age; AOR controlled for consumption of alcohol |
| Akiba and Hirayama 1990 | • 122,261 (men) and 142,857 (women) followed<br>• 1,050 cases (652 men and 398 women)<br>• 1965–1981<br>• Japan | • Current smoker:<br>– Men: 1.5 (1.2–1.9)<br>– Women: 1.6 (1.2–2.0)<br>• Cigarettes/day, men:<br>– 1–4: 1.1 (0.5–2.0)<br>– 5–14: 1.6 (1.3–2.0)<br>– 15–24: 1.4 (1.2–1.8)<br>– 25–34: 1.6 (1.1–2.4)<br>– ≥35: 1.9 (1.1–3.2)<br>– p trend = 0.002<br>• Cigarettes/day, women:<br>– 1–4: 1.4 (0.7–2.5)<br>– 5–14: 1.4 (1.0–2.0)<br>– ≥15: 2.5 (1.3–4.1)<br>– p trend = 0.001 | Adjusted for prefecture, occupation, age, and observation period; no trend in risk observed in relation to calendar period |
| Hsing et al. 1990 | • Study among military veterans<br>• 250,000 followed<br>• 289 cases<br>• 1954–1980<br>• United States | • Current smokers: 2.4 (1.6–3.5)<br>• Former smokers, not current cigar/pipe: 1.9 (1.2–2.9)<br>• Cigar/pipe smokers: 3.1 (2.0–4.8)<br>• Cigarettes/day:<br>– <10: 2.2 (1.2–3.8)<br>– 10–20: 2.0 (1.3–3.0)<br>– 21–39: 2.9 (1.8–4.5)<br>– >39: 3.8 (1.9–8.0)<br>• Duration (years):<br>– <35: 0.9 (0.4–2.1)<br>– 35–39: 2.6 (1.4–4.9)<br>– >39: 2.7 (1.5–4.9)<br>• Age started smoking (years):<br>– <20: 2.9 (1.6–5.3)<br>– 20–24: 2.3 (1.2–4.3)<br>– >24: 1.0 (0.4–2.3) | Adjusted for age and calendar period; risks increased with the number of cigarettes/day, duration of smoking >35 years, and earlier age at initiation; did not control for consumption of alcohol or HBV status |
| Shibata et al. 1990 (Cohort I) | • 639 followed (all men)<br>• 22 cases<br>• 1958–1986<br>• Japan | • Current smoker: 1.1 (0.2–4.7)<br>• Cigarettes/day:<br>– 1–9: 0.6 (0.1–3.7)<br>– ≥10: 1.2 (0.2–5.7)<br>– p trend = ~0.6 | Adjusted for age; calculations based on small number of liver cancers; no information on HBV/HCV |

**Table 6.4*S* Continued**

| Study | Design/population | Findings (95% CI)[a] | Comments |
|---|---|---|---|
| Shibata et al. 1990 (Cohort II) | • 677 followed (all men)<br>• 22 cases<br>• 1960–1986<br>• Japan | • Former smoker: 2.9 (0.3–29.0)<br>• Current smoker: 3.6 (0.6–22.3)<br>• Cigarettes/day:<br>– 1–9: 11.9 (1.5–96.8)<br>– 10–19: 1.1 (0.1–10.6)<br>– 20–29: 2.7 (0.4–19.2)<br>– ≥30: 3.2 (0.4–23.7)<br>– p trend = ~0.5<br>• Consumers of alcohol, number of cigarettes/day:<br>– 1–19: 2.1 (0.4–10.0)<br>– ≥20: 1.9 (0.4–9.4) | Adjusted for age and consumption of alcohol |
| Kato et al. 1992 | • Participants with chronic hepatitis or cirrhosis<br>• 1,441 followed<br>• 122 cases<br>• 1987–1990<br>• Japan | • Former smoker: 0.9 (0.4–2.0)<br>• Current smoker: 1.0 (0.5–1.8)<br>• Pack-years:<br>– <30: 0.8 (0.4–1.7)<br>– ≥30: 0.9 (0.5–1.9)<br>– p trend = 0.824 | Adjusted for age and gender |
| Ross et al. 1992 | • Nested case-control study of males<br>• 18,244 followed<br>• 22 cases<br>• 1986–1989<br>• China | • Ever smoker: 1.8 (0.6–5.6)<br>• Cigarettes/day:<br>– 1–19: 3.1 (1.0–10.3)<br>– ≥20: 2.1 (0.6–6.9)<br>• Duration (years):<br>– 1–29: 2.6 (0.7–9.4)<br>– ≥30: 2.5 (0.9–7.6) | Population-based controls matched on age, sample collection date, and residence; analysis of ever smokers adjusted for age, education level, residence, HBsAg positivity, exposure to aflatoxin, and heavy consumption of alcohol |
| Tsukuma et al. 1993 | • Participants were patients with chronic liver disease<br>• 917 followed<br>• 54 cases<br>• 1987–1991<br>• Japan | • Current smoker: 2.3 (0.9–5.9)<br>• Former smoker: 1.7 (0.6–4.5) | Adjusted for age, gender, disease stage, alpha-fetoprotein level, and consumption of alcohol |
| Yu and Chen 1993 | • Nested case-control study<br>• 9,691 followed (all men)<br>• 35 cases<br>• 1987–1990<br>• China, Province of Taiwan | • Ever smoker: 1.2 (0.4–3.1) | Controls matched by age, date of interview, and residence; adjusted for testosterone level, consumption of alcohol, HCV/HBsAg status, consumption of vegetables, and history of liver disease |
| Chang et al. 1994 | • Nested case-control study<br>• 9,775 followed<br>• 38 cases<br>• 1984–1992<br>• China, Province of Taiwan | • Ever smoker: 1.2 (0.6–2.7) | Controls matched for age, residence, and date of recruitment |

**Table 6.4*S* Continued**

| Study | Design/population | Findings (95% CI)[a] | Comments |
|---|---|---|---|
| Doll et al. 1994 | • 34,439 followed (all men)<br>• 76 cases<br>• 1951–1991<br>• United Kingdom | • Annual mortality rate for liver cancer (per 100,000 men):<br>– Never smokers: 7<br>– Former smokers: 9<br>– Current smokers: 11<br>• Annual mortality rate for liver cancer (per 100,000 men), cigarettes/day:<br>– 1–14: 17<br>– 15–24: 3<br>– ≥25: 15<br>– p trend = 0.7 | No significant trend for the number of cigarettes/day |
| Goodman et al. 1995 | • Atomic bomb survivors<br>• 36,133 followed<br>• 242 cases<br>• 1978–1989<br>• Hiroshima and Nagasaki, Japan | • Ever smoker: 2.2 (1.5–3.2)<br>• Current smoker: 2.2 (1.5–3.2)<br>• Former smoker: 2.3 (1.5–3.6) | Adjusted for age, gender, and estimated radiation dose; no interaction with alcohol consumption and no dose-response relationship with smoking intensity or duration |
| London et al. 1995 | • Nested case-control study<br>• 60,984 followed (all men)<br>• 183 cases<br>• 1992–1995<br>• China | • Current smoker: 0.7 (0.5–1.0) | Controls matched 5:1 by age, area of residence, and HBV status; strong inverse association between recent hepatitis and current smoking |
| McLaughlin et al. 1995 | • United States veterans, 99.5% male<br>• 248,046 followed (all men)<br>• 363 cases<br>• 1954–1980<br>• United States | • Former smoker: 1.5 (1.2–2.0)<br>• Current smoker: 1.8 (1.4–2.3)<br>• Ever smoker: 1.7 (1.3–2.2)<br>• Cigarettes/day:<br>– 1–9: 1.8 (1.1–2.8)<br>– 10–20: 1.4 (1.1–2.0)<br>– 31–39: 2.3 (1.6–3.1)<br>– ≥40: 2.6 (1.4–4.6)<br>– p trend = <0.01 | Mortality study did not control for consumption of alcohol or viral status; adjusted for age and calendar year; increased risk with increased smoking intensity |
| Chen et al. 1996 | • 6,487 followed<br>• 33 cases<br>• 1991–1993<br>• Taiwan | • Ever smoker: 3.6 (1.3–10.6) | Age-gender-adjusted analysis was significant, but smoking was not included in the final model, which adjusted for HBV, HCV, aflatoxin exposure, and family history of HCC |
| Chiba et al. 1996 | • 249 men and 163 women followed<br>• 63 cases<br>• 1977–1993<br>• Japan | • <20 pack-years: 1.7 (0.8–3.7)<br>• ≥20 pack-years: 2.5 (1.1–5.5) | Adjusted for age, gender, consumption of alcohol, clinical stage of liver disease, serum alpha-fetoprotein value, HBV, history of blood transfusion, surgical procedures, and family history of liver cancer |
| Murata et al. 1996 | • 17,200 followed (all men)<br>• 9 cases<br>• 1983–1994<br>• Japan | • Cigarettes/day:<br>– 1–10: 1.4<br>– 11–20: 2.0, p <0.05<br>– ≥21: 0.4 | |

**Table 6.4*S* Continued**

| Study | Design/population | Findings (95% CI)[a] | Comments |
|---|---|---|---|
| Yuan et al. 1996 | • 18,244 followed (all men)<br>• 79 cases<br>• 1986–1993<br>• China | • Ever smoker: 1.8, p <0.05<br>• Cigarettes/day:<br>– <20: 1.8<br>– ≥20: 1.8 | Adjusted for age and consumption of alcohol |
| Chen et al. 1997 | • 6,494 men and 2,857 women followed<br>• 66 cases<br>• 1972–1993<br>• China | • Current smoker: 2.0 (p <0.05)<br>• Cigarettes/day:<br>– 1–19: 2.1<br>– ≥20: 2.1<br>– p trend = 0.07 | Adjusted for age, blood pressure, cholesterol, and consumption of alcohol at baseline |
| Lam et al. 1997 | • Chinese factory workers<br>• 1,124 men and 572 women followed<br>• 16 cases<br>• 1976–1996<br>• China | • Ever smoker, men: 1.1 (0.4–2.9) | Adjusted for age, marital status, occupation, blood pressure, triglycerides, and total cholesterol |
| Nordlund et al. 1997 | • 28,089 followed (all women)<br>• 41 cases<br>• 1963–1989<br>• Sweden | • Current smoker: 0.7 (0.2–2.0) | Adjusted for age and place of residence |
| Liaw and Chen 1998 | • 14,937 followed<br>• 128 cases<br>• 1982–1994<br>• Taiwan | • Current smoker, men: 2.2 (1.4–3.6)<br>• Cigarettes/day, men:<br>– ≤10: 2.1 (1.2–3.5)<br>– 11–20: 1.9 (1.2–3.2)<br>– >20: 1.8 (1.2–3.5)<br>– p trend = 0.02<br>• Duration (years), men:<br>– ≤20: 1.6 (0.8–3.2)<br>– 21–30: 1.0 (0.5–2.1)<br>– >30: 2.5 (1.6–4.1)<br>• Age (years) started smoking, men:<br>– >24: 1.4 (0.8–2.6)<br>– 21–24: 2.3 (1.2–4.2)<br>– ≤20: 2.2 (1.4–3.7)<br>– p trend = <0.01<br>• Pack-years, men:<br>– <20: 1.7 (1.0–2.9)<br>– 20–40: 2.1 (1.2–3.5)<br>– ≥41: 2.5 (1.3–4.6) | Adjusted for age, gender, alcohol intake, and HBsAg status; risk rose with increased pack-years, >30 years duration, and initiation at <25 years of age; inverse trend seen with number of cigarettes/day; study partially overlapped with Wen et al. (2004) |
| Liu et al. 1998 | • Retrospective proportional mortality study<br>• 21,457 followed<br>• 87,215 cases<br>• 1989–1991<br>• China | • Ever smoker:<br>– Men: 1.4 (1.3–1.5)<br>– Women: 1.2 (1.1–1.3) | Estimates of risk ratio (standard error) after adjustment for age and study area (county or city) |

**Table 6.4*S* Continued**

| Study | Design/population | Findings (95% CI)[a] | Comments |
|---|---|---|---|
| Gao et al. 1999 | • 213,800 followed<br>• 1983–1994<br>• China | • Ever smoker, men:<br>– Urban: 1.5[b]<br>– Suburban: 1.4<br>– Rural: 1.5[b]<br>• Ever smoker, women (urban): 2.4 | p trend = <0.05 for smoking intensity for men and women and for age at initiation among men only |
| Sun et al. 1999 | • Subjects were all HBsAg positive<br>• 145 followed (all men)<br>• 10 cases<br>• 1987–1998<br>• China | • Incidence rate/100 person-years:<br>– Never smoker: 2.3<br>– Current smoker: 1.6<br>– p = 0.5 | |
| Mizoue et al. 2000 | • 4,050 followed (all men)<br>• 59 cases<br>• 1986–1996<br>• Japan | • Former smoker: 2.9 (1.0–8.4)<br>• Current smoker: 3.3 (1.2–9.5)<br>• Cigarettes/day:<br>– 1–24: 3.5 (1.2–10.2)<br>– ≥25: 2.8 (0.8–9.6) | Adjusted for age, area of residence, and consumption of alcohol; no dose-response effect with smoking intensity |
| Mori et al. 2000 | • 3,052 followed<br>• 22 cases<br>• 1992–1997<br>• Japan | • Ever smoker: 2.1 (0.6–7.2)<br>• Pack-years:<br>– <10: 3.3 (0.4–28.2)<br>– ≥10: 2.0 (0.6–6.9)<br>– p trend = 0.3 | Adjusted for age and gender |
| Evans et al. 2002 | • 48,454 men and 25,430 women followed<br>• 977 cases<br>• 1992–2000<br>• China | • Current smoker (age adjusted):<br>– Men: 0.9 (0.8–1.1)<br>– Women: 2.0 (0.9–4.2)<br>• Female (multivariate), cigarettes/day:<br>– 1–5: 1.5 (0.4–6.3)<br>– 6–10: 2.0 (0.6–6.5)<br>– ≥10: 4.2 (1.3–13.8) | Adjusted for HBV and consumption of alcohol among women; no interaction between HBsAg status and cigarette smoking; smoking was not significantly associated with liver cancer and was excluded from multivariate model in men; dose-response association in women |
| Yang et al. 2002 | • Nested case-control study<br>• 1,183 followed (all men)<br>• 111 cases<br>• 1991–2000<br>• Taiwan | • Ever smoker: 1.5 (1.0–2.2) | Population-based controls matched on age, date of enrollment, and township; adjusted for age, consumption of alcohol, and HBV/HCV status |
| Wang et al. 2003 | • 11,837 followed; 115 cases<br>• 1991–2000<br>• Taiwan | • Ever smoker: 1.5 (1.1–2.3)<br>• HBV negative: 2.5 (1.0–6.1)<br>• HBV positive: 1.4 (0.9–2.2) | Adjusted for age, residence, and HBV and HCV infection |
| Jee et al. 2004 | • 1,283,112 followed<br>• 3,807 cases<br>• 1993–2002<br>• Republic of Korea | • Current smoker:<br>– Male: 1.5 (1.3–1.7)<br>– Female 1.1 (0.8–1.7)<br>• Former smoker:<br>– Male: 1.1 (1.0–1.3)<br>– Female: 1.3 (0.8–2.1)<br>• Ever smoker, male:<br>– HBsAg positive: 29.0 (23.7–35.4)<br>– HBsAg negative: 1.1 (0.9–1.4) | Adjusted for age, consumption of alcohol, diabetes, and HBsAg; no interaction between smoking, consumption of alcohol, and HBsAg |

**Table 6.4*S* Continued**

| Study | Design/population | Findings (95% CI)[a] | Comments |
|---|---|---|---|
| Ogimoto et al. 2004 | • 65,528 followed<br>• 186 cases<br>• 1988–1999<br>• Japan | • Current smoker, men (age):<br>– 40–59: 2.0 (0.8–5.1)<br>– 60–69: 2.6 (1.2–5.8)<br>• Current smoker, women (age):<br>– 40–59: 2.8 (0.6–13.1)<br>– 60–69: 1.5 (0.5–4.9)<br>• Former smoker, men (age):<br>– 40–59: 2.4 (0.8–6.8)<br>– 60–69: 2.7 (1.2–6.1)<br>• Former smoker, women (age)<br>– 60–69: 1.2 (0.2–8.7) | No adjustments; 15–19 years of age at smoking initiation increased HR from 4 to 8 for current and former smokers |
| Wen et al. 2004 | • 86,580 followed<br>• 245 cases<br>• 1982–2000<br>• Taiwan | • Current smoker:<br>– Men: 1.5 (1.2–1.8)<br>– Women: 5.0 (2.4–10.7) | Adjusted for age |
| Yun et al. 2005 | • 733,134 followed (men)<br>• 1,434 cases<br>• 1996–2000<br>• Republic of Korea | • Current smoker: 1.5 (1.3–1.7) | Adjusted for age, residence, consumption of alcohol, physical activity, BMI, and diet; no trend with increasing duration of smoking |
| Fujita et al. 2006 | • 110,792 followed<br>• 58 cases<br>• 1988–1999<br>• Japan | • Current smokers:<br>– HCV-positive: OR = 9.6 (1.5–61.4)<br>– HCV-negative: OR = 1.7 (0.6–5.1)<br>• Former smokers:<br>– HCV-positive: OR = 7.8 (1.1–56.0)<br>– HCV-negative: OR = 0.3 (0.0–1.7) | Adjusted for age, gender, diabetes, liver disease, and consumption of alcohol |
| Chen et al. 2006 | • 3,653 followed (men)<br>• 164 cases<br>• Taiwan<br>• 1991–1992 | • Ever smoker:<br>– Crude: 1.7 (1.2–2.3)<br>– HBsAg positive: 1.0 (0.7–1.4)<br>– HBsAg negative: 0.9 (0.6–1.4) | Participants were all HBsAg positive; adjusted for age, gender, consumption of alcohol, liver disease, and HBV virologic markers |
| Ikeda et al. 2007 | • 846 followed (men)<br>• 237 cases<br>• 1995–2005<br>• Japan | • Persons with chronic hepatitis C:<br>– <20 pack-years: IRR = 1.8 (1.1–3.3)<br>– ≥20 pack-years: IRR = 2.1 (1.2–3.6)<br>• Persons with HCV-related cirrhosis:<br>– <20 pack-years: IRR = 1.1 (0.7–1.9)<br>– ≥20 pack-years: IRR = 1.1 (0.7–1.7) | Participants had HCV-related chronic hepatitis or cirrhosis; adjusted for consumption of alcohol, age, gender, and HBV/HCV therapy |
| Ohishi et al. 2008 | • Nested case-control study of atomic bomb survivors<br>• 20,000 followed<br>• 224 cases<br>• 1970–2002<br>• Japan | • Current smoker: 2.0 (0.8–5.0)<br>• Former smoker: 1.1 (0.3–5.2) | Matched on age, gender, and city; adjusted for consumption of alcohol and coffee, BMI, diabetes, HBV/HCV markers, and estimated radiation dose |

**Table 6.4*S* Continued**

| Study | Design/population | Findings (95% CI)[a] | Comments |
|---|---|---|---|
| Chen et al. 2008 | • 23,567 followed<br>• 291 cases<br>• 1991–2004<br>• Taiwan | • HBV/HCV negative (comparisons with never smokers):<br>– Current smoker: 2.4 (1.2–5.0)<br>– Former smoker: 1.0 (0.2–4.6)<br>• HBV positive (comparisons with never smokers):<br>– Current smoker: 1.1 (0.8–1.5)<br>– Former smoker: 1.0 (0.5–2.0)<br>• HCV positive (comparisons with never smokers):<br>– Current smoker: 1.4 (0.6–3.3)<br>– Former smoker: 2.9 (0.9–9.1) | Adjusted for age and gender |
| Di Costanzo et al. 2008 | • Retrospective cohort of post transfusion, HCV-infected cirrhotic patients<br>• 138 followed<br>• 63 cases<br>• 1994–2004<br>• Italy | • Smoker: HR = 1.4 (0.80–2.3) | Adjusted for age, gender, diabetes, consumption of alcohol, and interferon therapy |
| Lok et al 2009 | • HCV-infected patients with significant fibrosis or cirrhosis at baseline<br>• 1,005 followed<br>• 48 cases<br>• 2001–2007<br>• United States | • Ever smoker: HR = 2.1 (p = 0.07) | Adjusted for age, race, alkaline phosphatase, des-carboxy prothrombin level, cirrhosis, esophageal varices, randomization group, and aspartate aminotransferase/platelet ratio index |
| Koh et al. 2011 | • 61,321 followed<br>• 394 cases<br>• 1993–2007<br>• Singapore | • Smokers:<br>– Current smoker: HR = 1.6 (1.3–2.1)<br>– Former smoker: HR = 1.1 (0.8–1.5)<br>• Cigarettes/day among current smokers:<br>– 1–12: HR = 1.53 (1.10–2.12)<br>– >12 (86 cases): HR = 1.72 (1.28–2.30)<br>• Years of smoking:<br>– <20: HR = 1.1 (0.7–1.8)<br>– ≥20: HR = 1.5 (1.2–1.9)<br>• Pack-years of smoking:<br>– <20: HR = 1.2 (0.9–1.7)<br>– 20–39: HR = 1.5 (1.2–2.0)<br>– ≥40: HR = 1.5 (1.1–2.2)<br>• Results were similar when daily drinkers were excluded from the analysis.<br>• P values for trend were significant for number of cigarettes/day, years of smoking, and pack-years of smoking<br>• Among HBV- and HCV- participants, ever smoking was associated with a nonsignificant increased risk for HCC in all strata of alcohol consumption | Adjusted for age, gender, year of recruitment, dialect group, education level, BMI, diabetes, daily ethanol intake and coffee intake |

**Table 6.4*S* Continued**

| Study | Design/population | Findings (95% CI)[a] | Comments |
|---|---|---|---|
| Trichopoulos et al. 2011 | • Nested case-control study<br>• Estimated 500,000 followed<br>• 115 cases<br>• 1992–2006<br>• Europe | • All subjects:<br>– Current smoker: 4.6 (1.9–10.9)<br>– Former smoker: 2.0 (0.90–4.4)<br>• Men:<br>– Current smoker: 5.4 (1.7–16.8)<br>– Former smoker: 1.7 (0.6–4.9)<br>• Women:<br>– Current smoker: 1.7 (0.3–8.5)<br>– Former smoker: 1.4 (0.3–6.0) | Matched by study site, age, gender, and calendar time of recruitment; women matched on menopausal status; adjusted for HBV/HCV status, education level, ethanol and coffee intake, and BMI |
| Kusakabe et al. 2011 | • HBV-infected patients<br>• 479 followed<br>• 13 cases<br>• 1993–2006<br>• Japan | • Current smoker: HR = 2.8 (0.6–13) | Adjusted for age, gender, BMI, consumption of alcohol, levels of liver enzymes, and HBV molecular characteristics |
| Oh et al. 2012 | • 6,694 followed<br>• 50 cases<br>• 1993–2003<br>• Republic of Korea | • Current smoker: HR = 1.3 (0.6–2.6)<br>• Former smoker: HR = 1.2 (0.4–3.3) | Models with smoking estimates did not include data pertaining to HBV and HCV; adjusted for age and gender only |
| Sahasrabuddhe et al. 2012 | • 300,504 adults, 50–71 years of age, followed<br>• 250 cases<br>• 1995–2006<br>• United States | • Former smokers, by cigarettes/day:<br>– ≤20: HR = 1.2 (0.9–1.7)<br>– >20: HR = 1.3 (0.9–1.9)<br>• Current smokers, by cigarettes/day:<br>– ≤20: HR = 2.4 (1.5–3.8)<br>– >20: HR = 1.8 (1.0–3.4) | Unadjusted models |

*Notes:* **BMI** = body mass index; **CI** = confidence interval; **HBsAg** = hepatitis B surface antigen; **HBV** = hepatitis B virus; **HCV** = hepatitis C virus; **HR** = hazard ratio; **IRR** = incident rate ratio; **OR** = odds ratio; **pack-years** = the number of years of smoking multiplied by the number of packs of cigarettes smoked per day; **person-years** = the sum of the number of years that each member of a population has been smoking.
[a]Findings are reported as relative risks and compared with never smokers, unless indicated otherwise.
[b]CI does not include 1.0.

**Table 6.5*S*  Prospective studies of cigarette smoking and colorectal cancer incidence, published 2002–2009**

| Study | Design/population | Findings (95% CI) | Adjustment(s) | Comments |
|---|---|---|---|---|
| Terry et al. 2002b | • 89,835 women<br>• 40–59 years of age at entry in 1980<br>• 363 colon cases; 164 rectal cases<br>• Canada<br>• 10.6 years follow-up | • Colorectal:<br>– Current smokers: rate ratio = 1.0 (0.80–1.26)<br>– Former smokers: rate ratio = 1.15 (0.94–1.41)<br>• Rectal cancer:<br>– 30–39 years since smoking initiation: rate ratio = 1.52 (95% CI, 1.01–1.26)[a]<br>– ≥40 years since smoking initiation: rate ratio = 2.27 (95% CI, 1.06–4.87) | Age, BMI, education, physical activity, other | NA |
| Tiemersma et al. 2002 | • DCMP<br>• 36,000 men and women enrolled<br>• 1987–1991<br>• 20–59 years of age<br>• Case cohort: 102 cases; 537 controls<br>• 8.5 years follow-up | • Duration of smoking (current smokers):<br>– 1–15 years: OR = 1.0<br>– 16–30 years: OR = 0.4 (0.1–1.9)<br>– >30 years: OR = 1.9 (0.5–8.2)<br>– p = 0.28<br>• Duration of smoking (former smokers):<br>– 1–15 years: OR = 1.0<br>– 16–30 years: OR = 2.7 (1.03–7.4)<br>– >30 years: OR = 3.2 (1.04–9.8)<br>– p = 0.04<br>• Trend significant for former smokers | Age, gender, coffee, alcohol, BMI | NA |
| Limburg et al. 2003 | • 34,467 women<br>• 55–69 years of age at baseline in 1986<br>• 869 colon, rectal, and colorectal cases<br>• 249 fatal<br>• United States | • Current smokers: RR = 1.10 (0.89–1.37)<br>• Former smokers: RR = 1.21 (1.01–1.45)<br>• Duration of smoking:<br>– 1–19 years: RR = 1.16 (0.89–1.52)<br>– 20–39 years: RR = 1.08 (0.88–1.32)<br>– ≥40 years: RR = 1.30 (1.04–1.63)<br>• Increasing duration of smoking significantly related to risk of colorectal cancer incidence (p = 0.03) | Age, BMI, physical activity, alcohol, other | NA |
| Otani et al. 2003 | • 90,004 men and women<br>• 40–69 years of age in 1990<br>• 298 colorectal cases (invasive only)<br>• 299 colon cases (invasive and noninvasive); 148 rectal cases (invasive and noninvasive)<br>• Japan | • Current smokers:<br>– Colorectal: RR = 1.6 (1.1–2.1)<br>– Colon: RR = 1.4 (0.99–1.9)<br>– Rectal: RR = 1.4 (0.9–2.3) | Age, family history, BMI, physical activity, and study location | NA |
| Shimizu et al. 2003 | • 29,051 participants<br>• ≥35 years of age<br>• 1992 baseline data<br>• 104 colon cases in men; 57 rectal cases in men<br>• 77 colon cases in women; 38 rectal cases in women<br>• Japan<br>• 8 years follow-up | • Men (colon):<br>– ≤20 pack-years: RR = 1.36 (0.79–2.33)<br>– >20 pack-years: RR = 1.37 (0.81–2.32)<br>• Men (rectal):<br>– ≤20 pack-years: RR = 1.33 (0.57–3.12)<br>– >20 pack-years: RR = 2.44 (1.12–5.30) | Age, height, BMI, alcohol, years education | NA |

**Table 6.5*S* Continued**

| Study | Design/population | Findings (95% CI) | Adjustment(s) | Comments |
|---|---|---|---|---|
| van der Hel et al. 2003 | • Diagnostisch Onderzoek Mammacarcinoom<br>• 27,222 women<br>• 249 colorectal cases (183 colon, 66 rectal)<br>• The Netherlands<br>• Follow-up 1987–1996 | • Ever smokers:<br>– Colon: RR = 1.36 (0.97–1.92)<br>– Rectal: RR = 1.31 (0.76–2.25) | Age, BMI | NA |
| Wakai et al. 2003 | • JACC<br>• 25,260 men and 34,619 women<br>• 40–79 years of age<br>• Recruited 1988–1990<br>• 408 colon cases; 204 rectal cases<br>• Japan<br>• 7.6 years follow-up | • Men (colon):<br>– Current smokers: HR = 1.23 (0.85–1.78)<br>– Former smokers: HR = 1.07 (0.72–1.59)<br>• Men (rectal):<br>– Current smokers: HR = 0.83 (0.55–1.26)<br>– Former smokers: HR = 0.88 (0.56–1.39)<br>• Women (colon):<br>– Current smokers: HR = 1.06 (0.55–2.02)<br>– Former smokers: HR = 1.07 (0.39–2.92)<br>• Women (rectal):<br>– Current smokers: HR = 0.36 (0.05–2.65)<br>– Former smokers: HR = 1.05 (0.14–7.69)<br>• Number of years of smoking not related to risk (p = 0.52)<br>• Cumulative amount smoked not related to risk (p = 0.90) | Age, education, family history, alcohol, diet, other | NA |
| Sanjoaquin et al. 2004 | • Oxford Vegetarian Study<br>• 11,140 participants<br>• 16–89 years of age<br>• 1980–1984<br>• Colorectal cases: 16 (current smokers), 43 (former smokers), and 36 (never smokers)<br>• United Kingdom<br>• 17 years follow-up | • Current smokers: RR = 1.88 (1.03–3.44)<br>• Former smokers: RR = 1.95 (1.24–3.07) | Age, gender | NA |
| Lüchtenborg et al. 2005 | • Netherlands Cohort Study on Diet and Cancer<br>• 58,279 men and 62,573 women<br>• 50–69 years of age at entry in 1986<br>• 661 colorectal cases (excluding the first 2.3 years of follow-up)<br>• The Netherlands<br>• 7.3 years follow-up | • Current smokers: IRR = 0.91 (0.71–1.18)<br>• Former smokers: IRR = 1.30 (1.03–1.65)<br>• No significant trend for age at smoking initiation or duration of smoking | Age, gender, family history, BMI | Weijenberg and colleagues (2008) have updated cohort analysis for *KRAS* oncogene mutation with fewer cases |

**Table 6.5*S* Continued**

| Study | Design/population | Findings (95% CI) | Adjustment(s) | Comments |
|---|---|---|---|---|
| Yun et al. 2005 | • Korean National Health Insurance Corporation<br>• 733,134 men<br>• ≥30 years of age in 1996<br>• Current smokers: 42.4 years of age (mean)<br>• Former smokers: 44.7 years of age (mean)<br>• 417 colon cases; 453 rectal cases<br>• Republic of Korea<br>• Followed through 2000 | • Colon:<br>– Current smokers: RR = 0.81 (0.63–1.05)<br>– Former smokers: RR = 1.37 (1.06–1.77)<br>• Rectal:<br>– Current smokers: RR = 0.97 (0.76–1.24)<br>– Former smokers: RR = 1.17 (0.91–1.52) | Age, alcohol, BMI, physical activity, diet | NA |
| Berndt et al. 2006 | • CLUE II<br>• 22,887 residents<br>• 250 colorectal cases<br>• Washington County, Maryland | • Ever smokers: IRR = 1.23 (0.91–1.66) | Age, gender | NA |
| Kim et al. 2006 | • 14,103 men and women<br>• 100 colorectal cases<br>• Republic of Korea | • Duration of smoking:<br>– ≤45 years: RR = 1.51 (0.97–2.34)<br>– >45 years: RR = 2.35 (1.16–4.74)<br>– p ≤0.01<br>• Duration of smoking related to risk | Age, gender, alcohol, BMI, other | NA |
| Akhter et al. 2007 | • 25,279 men<br>• 40–64 years of age in 1990<br>• 188 colorectal cases<br>• Japan<br>• 7 years follow-up | • Current smokers: RR = 1.47 (0.93–2.34)<br>• Former smokers: RR = 1.73 (1.04–2.87) | Age, family history, education, alcohol, diet, other | Age at smoking initiation significant trend (includes never smokers); duration of smoking significant trend (includes never smokers) |
| Driver et al. 2007 | • Physicians' Health Study<br>• 21,581 men<br>• 381 colon cases; 104 rectal cases<br>• United States<br>• 20 years follow-up | • Colorectal (ever smokers): OR = 1.42 (1.17–1.72)<br>• Colon:<br>– Current smokers (1 pack/day): OR = 1.06 (0.57–1.98)<br>– Current smokers (2 packs/day): OR = 1.53 (1.02–2.29)<br>– Former smokers: OR = 1.50 (1.19–1.89)<br>• Rectal:<br>– Current smokers (1 pack/day): OR = 0.85 (0.26–2.77)<br>– Current smokers (2 packs/day): OR = 1.92 (1.01–3.66)<br>– Former smokers: OR = 1.13 (0.73–1.75) | Age, BMI, alcohol, physical activity, other | Smoking collapsed to ever smokers for combined colorectal cancer then evaluated as current smokers and former smokers by site |

**Table 6.5*S* Continued**

| Study | Design/population | Findings (95% CI) | Adjustment(s) | Comments |
|---|---|---|---|---|
| Paskett et al. 2007 | • Women's Health Initiative<br>• 146,877 women<br>• 50–79 years of age in 1994<br>• 1,242 colorectal cases: 1,075 colon, 176 rectal<br>• United States<br>• 7.8 years follow-up | • Colon:<br>– Current smokers: HR = 1.03 (0.77–1.38)<br>– Former smokers: HR = 1.12 (0.97–1.29)<br>• Rectal:<br>– Current smokers: HR = 1.95 (1.10–3.47)<br>– Former smokers: HR = 1.15 (0.80–1.67)<br>• Duration of smoking:<br>– Colon<br>o <20 years: HR = 0.95 (0.79–1.15)<br>o 20–29 years: HR = 1.27 (1.02–1.58)<br>o 30–39 years: HR = 1.18 (0.93–1.50)<br>o ≥40 years: HR = 1.19 (0.93–1.54)<br>– Rectum<br>o <20 years: HR = 0.87 (0.52–1.43)<br>o 20–29 years: HR = 1.95 (1.20–3.17)<br>o 30–39 years: HR = 1.24 (0.68–2.27)<br>o ≥40 years: HR = 1.53 (0.83–2.83)<br>• Current smokers had a significantly increased risk of rectal cancer | Age, ethnicity, study arm, alcohol, diet, physical activity, family history | NA |
| Tsong et al. 2007 | • 61,321 men and women<br>• 45–74 years of age<br>• Recruited 1993–1998<br>• 845 colorectal cases: 516 colon, 329 rectal<br>• Singapore<br>• 11 years follow-up | • Colon:<br>– Current smokers: HR = 0.83 (0.64–1.06)<br>– Former smokers: HR = 0.96 (0.73–1.27)<br>• Rectal:<br>– Current smokers: HR = 1.63 (1.23–2.17)<br>– Former smokers: HR = 1.45 (1.04–2.01) | Age, gender, education, BMI, family history, alcohol, physical activity | Age at smoking initiation related to rectal cancer but not colon cancer; duration of smoking related to rectal cancer but not colon cancer |
| Hooker et al. 2008 | • 91,908 households in 1963 census: 20,926 men; 24,823 women<br>• 90,225 households in 1975 census: 21,780 men; 26,372 women<br>• Rectal cancer incidence<br>• Washington County, Maryland | • Men (1963 cohort):<br>– Current smokers: RR = 3.05 (1.19–7.82)<br>– Former smokers: RR = 2.63 (0.98–7.05)<br>• Men (1975 cohort):<br>– Current smokers: RR = 1.80 (0.88–3.67)<br>– Former smokers: RR = 1.92 (0.98–3.78)<br>• Women (1963 cohort):<br>– Current smokers: RR = 0.93 (0.48–1.80)<br>– Former smokers: RR = 0.62 (0.19–2.08)<br>• Women (1975 cohort):<br>– Current smokers: RR = 1.57 (0.89–3.76)<br>– Former smokers: RR = 1.87 (1.02–3.45) | Age, education, marital status | NA |
| Gram et al. 2009 | • 68,160 women<br>• 30–69 years of age at enrollment in 1996–1998<br>• 425 colorectal cases: 284 colon, 141 rectal<br>• Norway<br>• Followed through 2005 | • Ever smokers:<br>– Colorectal: rate ratio = 1.2 (1.0–1.5)<br>– Colon: rate ratio = 1.3 (1.0–1.7)<br>– Rectal: rate ratio = 1.1 (0.7–1.5)<br>• Years smoked significant for colorectal cancer (p = 0.04)<br>• No significant trends for individual sites<br>• Pack-years smoked significant for colorectal cancer (p = 0.008) | Age, menopausal status, BMI, alcohol, hormone therapy | NA |

**Table 6.5*S* Continued**

| Study | Design/population | Findings (95% CI) | Adjustment(s) | Comments |
|---|---|---|---|---|
| Hannan et al. 2009 | • Cancer Prevention Study II<br>• 184,187 men and women<br>• 50–74 years of age<br>• 1,962 colorectal cases<br>• 1992–2005 study period | • Current smokers: HR = 1.27 (1.06–1.52)<br>• Former smokers: HR = 1.23 (1.11–1.36)<br>• Among current smokers, relative risk greatest for current smokers of long duration (p = 0.052)<br>• Risk comparable in both men and women | Age, BMI, education, family history, physical activity, race, aspirin, alcohol, other | NA |

*Notes:* **BMI** = body mass index; **CI** = confidence interval; **CLUE II** = Campaign Against Cancer and Heart Disease; **DCMP** = Dutch Cardiovascular Monitoring Project; **HR** = hazard ratio; **IRR** = incidence rate ratio; **JACC** = Japanese Collaborative Cohort Study for Evaluation of Cancer Risk; **NA** = not applicable; **OR** = odds ratio; **pack-years** = the number of years of smoking multiplied by the number of packs of cigarettes smoked per day; **RR** = relative risk.
[a]The RR does not fall within the CI. The information presented here appears just as it does on page 481 of Terry and colleagues (2002).

**Table 6.6*S*  Case-control studies of cigarette smoking and colorectal cancer incidence, published 2001–2008**

| Study | Design/population | Findings (95% CI) | Adjustment(s) | Comments |
|---|---|---|---|---|
| Chiu et al. 2001 | • 655 colon cases<br>• 629 rectal cases<br>• 2,336 controls<br>• Iowa | • Men (colon):<br>– Ever smokers: 1.3 (1.0–1.8)<br>– Former smokers: 1.5 (1.1–2.0)<br>– Current smokers: 1.0 (0.7–1.5)<br>• Men (rectal):<br>– Ever smokers: 1.3 (1.0–1.8)<br>– Former smokers: 1.4 (1.0–1.8)<br>– Current smokers: 1.3 (0.9–1.9)<br>• Women (colon):<br>– Ever smokers: 1.3 (0.9–1.7)<br>– Former smokers: 1.6 (1.1–2.2)<br>– Current smokers: 1.0 (0.7–1.4)<br>• Women (rectal):<br>– Ever smokers: 1.0 (0.7–1.3)<br>– Former smokers: 1.2 (0.8–1.8)<br>– Current smokers: 0.7 (0.5–1.1) | Age, total energy in dietary intake, other | NA |
| Ji et al. 2002 | • 1,805 cases (colon and rectal)<br>• 1,552 controls<br>• China | • Men (colon):<br>– Current smokers: 0.8 (0.6–1.0)<br>– Former smokers: 0.9 (0.6–1.3)<br>• Men (rectal):<br>– Current smokers: 0.9 (0.7–1.2)<br>– Former smokers: 1.1 (0.7–1.6)<br>• Women (colon):<br>– Current smokers: 0.6 (0.4–1.0)<br>– Former smokers: 0.6 (0.3–1.5)<br>• Women (rectal):<br>– Current smokers: 0.9 (0.5–1.3)<br>– Former smokers: 1.4 (0.7–3.0)<br>• No significant trend for RRs according to duration of smoking or pack-years among men and women | Age, alcohol, other | NA |
| Diergaarde et al. 2003 | • 176 colorectal cases<br>• 249 controls<br>• Europe | • Ever smokers: 1.00 (0.60–1.50) | Age, gender, alcohol | NA |
| Kim et al. 2003 | • 125 colorectal cases<br>• 245 controls<br>• Republic of Korea | • Ever smokers: 1.53 (0.94–2.52) | Age, gender, BMI, diet, alcohol, other | NA |
| Minami and Tateno 2003 | • 488 cases (colon and rectal)<br>• 2,444 controls<br>• Japan | • Ever smokers:<br>– Colon: 0.97 (0.71–1.33)<br>– Rectal: 1.65 (1.07–2.55) | Age, gender, alcohol, family history, other | NA |
| Ho et al. 2004 | • 822 cases (colon and rectal)<br>• 926 controls<br>• Hong Kong, China | • Current smokers:<br>– Colon: 0.84 (0.58–1.21)<br>– Rectal: 1.44 (1.00–2.06)<br>• No significant trend with duration of smoking and cigarettes smoked/day | Age, gender, diet, alcohol, family history, physical activity, other | NA |
| Nkondjock and Ghadirian 2004 | • 402 colon cases<br>• 688 controls<br>• Canada | • No statistically significant differences between cases and controls | NR | No data presented |

**Table 6.6*S* Continued**

| Study | Design/population | Findings (95% CI) | Adjustment(s) | Comments |
|---|---|---|---|---|
| Ates et al. 2005 | • 181colorectal cases<br>• 204 controls<br>• Europe/Turkey | • Ever smokers: 1.43 (0.94–2.18) | Age, gender | After reporting, main effect analysis focuses on *GST* genotypes and risk |
| Jin et al. 2005 | • 140 colorectal cases<br>• 240 controls<br>• China | • Ever smokers: 0.67 (0.36–1.25) | Age, gender, alcohol, family history | NA |
| Chia et al. 2006 | • 1,792 colorectal cases<br>• 1,501 controls<br>• United States | • Ever smokers: 1.4 (1.2–1.6)<br>• Current smokers: 1.7 (1.4–2.1)<br>• Former smokers: 1.2 (1.1–1.4)<br>• Duration of smoking (>40 years): 1.6 (1.2–2.1)<br>• Significant trend with duration of smoking (p = 0.007) | Age, gender, BMI, family history, other | NA |
| Verla-Tebit et al. 2006 | • 540 colorectal cases<br>• 614 controls<br>• Germany | • Ever smokers: 1.01 (0.77–1.32) | Age, gender, BMI, diet, alcohol, family history, physical activity, other | NA |
| Gao et al. 2007 | • 315 cases (colorectal, colon, and rectal)<br>• 439 controls<br>• China | • Ever smokers:<br>– Colorectal: 1.01 (0.69–1.47)<br>– Colon: 0.84 (0.49–1.44)<br>– Rectal: 1.08 (0.70–1.67) | Age, gender, alcohol | NA |
| Hu et al. 2007 | • 1,723 colon cases<br>• 3,097 controls<br>• Canada | • Women (ever smokers):<br>– Proximal: 1.20 (0.90–1.50)<br>– Distal: 1.00 (0.80–1.20)<br>• Men (ever smokers):<br>– Proximal: 1.20 (0.90–1.60)<br>– Distal: 1.10 (0.90–1.40) | Age, BMI, physical activity, other | NA |
| Lüchtenborg et al. 2007 | • 1,959 colorectal cases<br>• 1,959 controls<br>• Hawaii | • Men:<br>– Current smokers: 1.32 (0.99–1.76)<br>– Former smokers: 1.21 (0.97–1.50)<br>• Women:<br>– Current smokers: 1.17 (0.85–1.62)<br>– Former smokers: 1.32 (1.02–1.71)<br>• Trend with duration of smoking and intensity not significant | Age, BMI, diet, physical activity, alcohol, family history, other | NA |
| Steinmetz et al. 2007 | • 674 colorectal cases<br>• 5,456 controls<br>• Europe | • Current smoker: RR = 1.42 (1.02–1.99)<br>• Former smoker: RR = 1.62 (1.28–10.08) | Age, alcohol, other | NA |
| Goy et al. 2008 | • 1,150 colon cases<br>• 1,549 controls<br>• Canada | • Current smokers: 0.86 (0.65–1.14)<br>• Former smokers:<br>– <10 years: 1.05 (0.78–1.43)<br>– >10 years: 1.18 (0.90–1.53) | Age, gender, BMI, diet | Not related to rectal cancer |

*Note:* Findings are presented as odds ratios unless indicated otherwise. **BMI** = body mass index; **CI** = confidence interval; **NA =** not applicable; **NR =** not reported; **pack-years** = the number of years of smoking multiplied by the number of packs of cigarettes smoked per day; **RR** = relative risk.

**Table 6.7*S* Prospective studies of cigarette smoking and colorectal cancer mortality, published 2002–2009**

| Study | Design/population | Findings (95% CI) | Adjustment(s) | Comments |
|---|---|---|---|---|
| Limburg et al. 2003 | • 34,467 women<br>• 55–69 years of age at baseline in 1986<br>• 249 cdolorectal deaths<br>• United States<br>• Followed through 1999 | • Current smokers: RR = 1.58 (1.09–2.29)<br>• Former smokers: RR = 1.14 (0.80–1.62)<br>• Duration of smoking:<br>– 1–19 years: RR = 1.53 (0.96–2.43)<br>– 20–39 years: RR = 1.02 (0.67–1.53)<br>– ≥40 years: RR = 1.55 (1.04–2.31)<br>• Increasing duration of smoking-related to increased risk of colorectal cancer mortality (p = 0.07) | Age, BMI, physical activity, alcohol, other | Cumulative pack-years (p trend = 0.05) |
| Colangelo et al. 2004 | • Chicago Heart Association Detection Project in Industry Study<br>• 39,299 men and women<br>• Recruited 1967–1973<br>• 208 colorectal deaths (men): 141 women<br>• 26 years follow-up | • Former smokers: RR = 0.97 (0.74–1.29) | Age, race, BMI, education, height, gender | Trend for cigarettes smoked/day significant in age-adjusted analysis, but not in multivariate analysis |
| Jee et al. 2004 | • 1,212,906 men and women<br>• 30–95 years of age<br>• Up to 511 cases<br>• Republic of Korea<br>• 9 years follow-up | • Current smokers: RR = 1.1 (0.8–1.4)<br>• Former smokers: RR = 1.1 (0.9–1.4) | NR | Most current smokers consumed less than 1 pack of cigarettes/day |
| Wen et al. 2004 | • 53,091 participants (combines two cohorts: 1982–1992 and 1989–1992)<br>• 45 colon deaths; 28 rectal deaths<br>• Taiwan | • Current smokers:<br>– Colon: RR = 0.84 (0.54–1.30)<br>– Rectal: RR = 2.06 (1.01–4.18) | NR | NA |
| Doll et al. 2005 | • 34,439 participants recruited in 1951<br>• 549 colon deaths; 201 rectal deaths<br>• Europe | • Significant trend for cigarettes smoked and risk of rectal cancer<br>• Relatively weak relationship between smoking and colorectal cancer<br>• Implausibly strong relationship between smoking and rectal cancer<br>• No relationship evident with smoking and colon cancer | NR | NA |
| Huxley 2007 | • 33 cohorts<br>• Asia<br>• 751 colorectal deaths<br>• 6.8 years follow-up (average) | • Ever smokers: HR = 1.43 (1.09–1.88) | Age, BMI, alcohol | NA |
| Ozasa 2007 | • JACC Study<br>• 607 cases<br>• Men: 200 colon deaths; 152 rectal deaths<br>• Women: 181 colon deaths; 74 rectal deaths<br>• Japan | • Current smokers (men):<br>– Colon: HR = 1.18 (0.80–1.72)<br>– Rectal: 1 HR = 0.31 (0.85–2.01)<br>• Current smokers (women):<br>– Colon: HR = 0.67 (0.29–1.53)<br>– Rectal: HR = 1.31 (0.52–3.29) | NR | NA |

**Table 6.7*S* Continued**

| Study | Design/population | Findings (95% CI) | Adjustment(s) | Comments |
|---|---|---|---|---|
| Batty et al. 2008 | • 17,322<br>• 40–69 years of age at baseline<br>• 309 colon deaths; 114 rectal deaths<br>• Europe | • Colon:<br>– Current smokers: HR = 1.33 (0.96–1.86)<br>– Former smokers: HR = 1.11 (0.80–1.55)<br>• Rectal:<br>– Current smokers: HR = 1.51 (0.84–2.74)<br>– Former smokers: HR = 1.94 (1.11–3.39) | NR | NA |
| Kenfield et al. 2008 | • Nurses' Health Study<br>• 104,519 women<br>• 34–59 years of age at baseline in 1980, when alcohol use and physical activity were ascertained<br>• 578 colorectal deaths<br>• 24 years follow-up | • Current smokers: HR = 1.63 (1.29–2.05)<br>• Former smokers: HR = 1.23 (1.02–1.49) | Age, BMI, alcohol, physical activity, other | Among current smokers, trend for cigarettes smoked/day significant in age-adjusted analysis (p = 0.02), but not significant in multivariate analysis |

*Note:* **BMI** = body mass index; **CI** = confidence interval; **HR** = hazard ratio; **JACC** = Japanese Collaborative Cohort Study for Evaluation of Cancer Risk; **NA =** not applicable; N**R =** not reported; **RR** = relative risk.

**Table 6.8*S*** **Prospective cohort studies on the association between cigarette smoking and prostate cancer incidence and mortality[a]**

| Study | Design/population | Findings by measure of smoking | |
|---|---|---|---|
| | | Incidence: RR (95% CI) | Mortality: RR (95% CI) |
| Hammond and Horn 1958 | • Hammond-Horn Study of the American Cancer Society<br>• 187,783 White men, 50–69 years of age<br>• 185 deaths<br>• 1952–1955<br>• United States | NR | • Age standardized<br>• Smoking status:<br>– Not regular: 1.00 (referent)<br>– Regular: 1.75 (ratio of observed to expected deaths)<br>– p = 0.05 |
| Hammond 1966 | • CPS-I of the American Cancer Society<br>• 440,558 men, 35–84 years of age<br>• 319 deaths<br>• 1959–1960<br>• United States | NR | • Age standardized<br>• Smoking status, 45–64 years of age:<br>– Never smoker: 1.00 (referent)<br>– Ever smoker: 1.04<br>• Smoking status, 65–79 years of age:<br>– Never smoker: 1.00 (referent)<br>– Ever smoker: 1.01 |
| Weir and Dunn 1970 | • 68,153 men, 35–64 years of age, who were members of a California labor union<br>• 37 deaths<br>• 1954–1962 | NR | • Age standardized<br>• Smoking status:<br>– Nonsmoker: 1.00 (referent)<br>– Smoker: 0.78<br>• Packs/day:<br>– Nonsmoker: 1.00 (referent)<br>– ≤0.5: 0.58<br>– 1: 0.98<br>– ≥1: 0.78 |
| Whittemore et al. 1984 | • Precursors study of 47,271 men who were alumni of Harvard University and University of Pennsylvania<br>• 243 cases<br>• 1962–1977 | • Adjusted for age, year, and school<br>• Smoking history: 1.1 (1.0–1.3) | NR |
| Carstensen et al. 1987 | • 25,129 Swedish men born between 1894–1945<br>• 193 deaths<br>• 1963–1979 | NR | • Age standardized<br>• Smoking status (pipe):<br>– Never smoker: 1.0 (referent)<br>– Former smoker: 1.0<br>– Current smoker (1–7 g/day of tobacco): 1.1<br>– Current smoker: (8–15 g/day): 0.8<br>– Current smoker: (>15 g/day): 0.9<br>– p trend = 0.7 |

**Table 6.8*S* Continued**

| Study | Design/population | Findings by measure of smoking | |
|---|---|---|---|
| | | Incidence: RR (95% CI) | Mortality: RR (95% CI) |
| Mills et al. 1989a<br>Additional information available in Mills and Beeson 1992 | • Approximately 14,000 men who were Seventh-day Adventists and residents of California<br>• 180 cases<br>• 1976–1982 | • Adjusted for age<br>• Smoking status:<br>– Never smoker: 1.00 (referent)<br>– Former smoker: 1.24 (0.91–1.67)<br>– Current smoker: 0.49 (0.16–1.57)<br>– p trend = 0.72<br>• Number of cigarettes/day:<br>– 0: 1.00 (referent)<br>– 1–14: 1.23 (0.84–1.81)<br>– ≥15: 1.18 (0.83–1.68)<br>– p trend = 0.32<br>• Smoking duration (years):<br>– 0: 1.00 (referent)<br>– <10: 1.07 (0.69–1.65)<br>– ≥10: 1.24 (0.89–1.72)<br>– p trend = 0.23 | NR |
| Severson et al. 1989 | • 7,999 men of Japanese ancestry, who were born between 1900 and 1919<br>• 1965–1986<br>• 174 Cases<br>• Oahu, Hawaii | • Adjusted for age<br>• Smoking status:<br>– Never smoker: 1.00 (referent)<br>– Former smoker: 0.89 (0.61–1.29)<br>– Current smoker: 0.87 (0.61–1.23) | NR |
| Thompson et al. 1989 | • 1,776 men, 50–84 years of age, who were residents of Rancho Bernardo, California<br>• 54 cases<br>• 1972–1987 | • Adjusted for multiple variables<br>• Smoking status:<br>– Not current: 1.0 (referent)<br>– Current: 1.3 (0.8–2.3) | • NR |
| Akiba and Hirayama 1990[b] | • Six-Prefecture Cohort Study<br>• 122,261 men, ≥40 years of age<br>• 255 deaths 1966–1981<br>• Japan | • NR | • Adjusted for age, residence, and year<br>• Number of cigarettes/day:<br>– Never smoker: 1.0 (referent)<br>– 1–4: 3.1 (1.4–6.4)<br>– 5–14: 1.0 (0.7–1.6)<br>– 15–24: 0.9 (0.6–1.4)<br>– 25–34: 0.8 (0.2–2.1)<br>– ≥35: 3.0 (1.0–7.1)<br>– ≥1 pack: 1.1 (0.7–1.5)<br>– p for trend >0.1 |

**Table 6.8*S* Continued**

| Study | Design/population | Findings by measure of smoking | |
|---|---|---|---|
| | | **Incidence: RR (95% CI)** | **Mortality: RR (95% CI)** |
| Hsing et al. 1990 | • 17,633 White men who held life insurance policies with the Lutheran Brotherhood Insurance Society<br>• 1966–1986<br>• 149 deaths<br>• United States | • NR | • Adjusted for age<br>• Smoking status:<br>– Never smoker: 1.0 (referent)<br>– Ever any form of tobacco: 1.8 (1.1–2.9)<br>– Pipes and/or cigars only: 1.6 (0.7–3.5)<br>– Cigarettes only: 2.0 (1.1–3.7)<br>– Smokeless tobacco only: 4.5 (2.1–9.7)<br>– Cigarettes and pipes and/or cigars: 1.7 (1.0–2.9)<br>– Cigarettes and smokeless tobacco: 2.9 (1.3–6.5)<br>– Smokeless tobacco and pipes and/or cigars: 1.4 (0.5–4.1)<br>– Cigarettes and smokeless tobacco and pipes and/or cigars: 1.6 (0.8–3.1)<br>• Number of cigarettes/day:<br>– Never smoker: 1.0 (referent)<br>– Occasional or former smoker: 1.9 (1.1–3.3)<br>– 1–19: 1.6 (0.8–3.3)<br>– 20–29:1.7 (0.8–3.5)<br>– ≥30: 1.4 (0.4–4.4) |
| Ross et al. 1990 | • 5,106 men who were residents of the Leisure World retirement community<br>• 138 cases<br>• 1964–1985<br>• Laguna Hills, California | • Adjusted for age<br>• Smoking status:<br>– Never smoker: 1.0 (referent)<br>– Former smoker: 0.8<br>– Current smoker: 0.9<br>• Number of cigarettes/day:<br>– 0: 1.0 (referent)<br>– 1–10: 0.9<br>– 11–20: 0.7<br>– 21: 0.7<br>• Smoking duration (years):<br>– Never: 1.0 (referent)<br>– 1–10: 2.2 (significant)<br>– 11–30: 0.8<br>– 31: 0.6<br>– p trend <0.02 | NR |

**Table 6.8*S* Continued**

| Study | Design/population | Findings by measure of smoking | |
|---|---|---|---|
| | | Incidence: RR (95% CI) | Mortality: RR (95% CI) |
| Hsing et al. 1991[c] | • 250,000 United States veterans who served in the armed forces between 1917–1940<br>• 4,607 deaths<br>• 1954–1980 | NR | • Adjusted for age<br>• Smoking status at 26-year follow-up:<br>– Never any tobacco: 1.00 (referent)<br>– Cigars and pipes only: 1.10 (0.99–1.22)<br>– Smokeless tobacco only: 1.17 (0.88–1.56)<br>– Former cigarette smoker: 1.13 (1.03–1.24)<br>– Current cigarette smoker: 1.18 (1.09–1.28)<br>• Smoking status at 26-year follow-up among current cigarette smokers by number of cigarettes/day:<br>– 1–9: 1.11 (0.97–1.27)<br>– 10–20: 1.15 (1.05–1.27)<br>– 21–39: 1.23 (1.09–1.38)<br>– >39: 1.51 (1.20–1.90)<br>– p trend <0.001<br>• Smoking duration (years):<br>– <25: 1.00 (referent)<br>– 25–29: 1.04 (0.74–1.47)<br>– 30–34: 0.92 (0.70–1.22)<br>– 35–39: 1.11 (0.87–1.42)<br>– >39: 1.23 (0.97–1.56)<br>– p trend <0.005<br>• Smoking status at 16-year follow-up:<br>– Never smoker: 1.00 (referent)<br>– Former smoker: 1.18<br>– Current smoker: 1.31<br>• Smoking status at 8.5-year follow-up:<br>– Never smoker: 1.00 (referent)<br>– Former smoker: 1.63<br>– Current smoker: 1.71<br>• Smoking status at 2.5-year follow-up:<br>– Nonsmoker: 1.00 (referent)<br>– Current smoker: 2.17 |

**Table 6.8*S* Continued**

| Study | Design/population | Findings by measure of smoking | |
|---|---|---|---|
| | | **Incidence: RR (95% CI)** | **Mortality: RR (95% CI)** |
| Tverdal et al. 1993<br><br>Additional information available in Thune and Lund 1994 | • 44,290 Norwegian men<br>• 1972–1988<br>• 32 deaths<br>• Oslo, Tromsø, Finnmark, Sogn og Fjordane, or Oppland, Norway | NR | • Adjusted for age and place of residence<br>• Smoking status (per 100,000 person years):<br>– Never smoker: 3.5<br>– Former smoker, cigarettes: 5.3<br>– Current smoker, pipe only: 2.3<br>– Current smoker, cigarettes only: 6.4<br>– Current smoker, pipe and cigarettes: 10.2<br>• Adjusted for multiple variables per 10 cigarettes/day: 0.6 (0.3–1.4) |
| Hiatt et al. 1994 | • 43,432 men, ≥30 years of age, who were members of the Kaiser Permanente Medical Care Program<br>• 238 cases<br>• 1979–1985<br>• Northern California | • Adjusted for multiple variables<br>• Smoking status:<br>– Never smoker: 1.0 (referent)<br>– Former smoker: 1.1 (0.8–1.5)<br>– <1 pack/day: 1.0 (0.6–1.6)<br>– ≥1 pack/day: 1.9 (1.2–3.1) | NR |
| Le Marchand et al. 1994 | • 20,316 men, ≥45 years of age, including Japanese, White, Filipino, Native Hawaiian, and Chinese<br>• 198 cases<br>• 1975–1989<br>• Hawaii | • Adjusted for age, ethnicity, and income<br>• Cigarettes/day by quartile (Q):<br>– Q1 (0): 1.0 (referent)<br>– Q2: 0.9 (0.6–1.4)<br>– Q3: 1.0 (0.7–1.6)<br>– Q4 (≥20): 1.0 (0.6–1.6)<br>– p trend = 0.92<br>• Pack-years of smoking by quartile (Q):<br>– Q1 (0): 1.0 (referent)<br>– Q2: 0.9 (0.5–1.5)<br>– Q3: 0.7 (0.4–1.2)<br>– Q4 (≥44): 1.2 (0.8–1.8)<br>– p trend = 0.69 | NR |
| Thune and Lund 1994<br><br>Additional information available in Tverdal et al. 1993 | • 42,067 Norwegian men<br>• 211 cases<br>• 1972–1991<br>• Oslo, Tromsø, Finnmark, Sogn og Fjordane, or Oppland, Norway | • Adjusted for age<br>• 10 cigarettes/day: 1.08 (0.90–1.30) | NR |

**Table 6.8*S* Continued**

| Study | Design/population | Findings by measure of smoking | |
|---|---|---|---|
| | | **Incidence: RR (95% CI)** | **Mortality: RR (95% CI)** |
| Adami et al. 1996 | • 135,006 Swedish male construction workers<br>• 2,368 cases<br>• 709 deaths<br>• 1971–1991 | • Adjusted for age<br>• Smoking status:<br>– Never smoker: 1.00 (referent)<br>– Former smoker: 1.09 (0.98–1.22)<br>– Current smoker: 1.11 (1.01–1.23)<br>• Number of cigarettes/day:<br>– 0: 1.00 (referent)<br>– 1–4: 1.06 (0.93–1.20)<br>– 5–14: 1.10 (0.99–1.31)<br>– 15–24: 1.14 (0.99–1.31)<br>– >25: 1.00 (0.72–1.38)<br>– p trend = 0.04<br>• Smoking duration (years):<br>– Former or never smoker: 1.00 (referent)<br>– 1–10: 1.20 (1.00–1.44)<br>– 11–20: 1.14 (0.97–1.34)<br>– >21: 1.03 (0.90–1.19)<br>– p trend = 0.33<br>• Smoking duration (years) among current smokers only:<br>– Never smoker: 1.00 (referent)<br>– 1–10: 0.68 (0.43–1.07)<br>– 11–20: 1.27 (1.02–1.58)<br>– 21–30: 1.09 (0.94–1.26)<br>– 31–40: 1.13 (1.01–1.28)<br>– >41: 1.07 (0.92–1.25)<br>– p trend = 0.05 | • Adjusted for age<br>• Smoking status:<br>– Never smoker: 1.00 (referent)<br>– Former smoker: 1.03 (0.84–1.33)<br>– Current smoker: 1.26 (1.06–1.50)<br>• Number of cigarettes/day:<br>– 0: 1.00 (referent)<br>– 1–4: 0.99 (0.78–1.26)<br>– 5–14: 1.13 (0.93–1.37)<br>– 15–24: 1.05 (0.82–1.35)<br>– p trend = 0.34<br>• Smoking duration (years):<br>– Former or never smoker: 1.00 (referent)<br>– 1–10: 1.12 (0.80–1.58)<br>– 11–20: 1.06 (0.78–1.44)<br>– >21: 0.98 (0.75–1.28)<br>– p trend = 0.96<br>• Smoking duration (years) among current smokers only:<br>– Never smoker: 1.00 (referent)<br>– 1–10 and 11–20 (combined): 1.41 (0.99–1.99)<br>– 21–30: 1.28 (0.98–1.67)<br>– 31–40: 1.19 (0.96–1.48)<br>– >41:1.28 (0.99–1.65)<br>– p trend = 0.03 |
| Coughlin et al. 1996 | • Multiple Risk Factor Intervention Trial<br>• 348,874 men, 35–57 years of age, who were screened for the trial<br>• 826 deaths<br>• 1973–1990<br>• United States | NR | • Adjusted for multiple variables<br>• Number of cigarettes/day:<br>– 0: 1.00 (referent)<br>– 1–15: 1.54 (p <0.01)<br>– 16–25: 1.27 (p <0.05)<br>– 26–35: 1.23<br>– 36–45: 1.50 (p <0.01)<br>– ≥46: 1.22<br>• Smoking status:<br>– Nonsmoker: 1.00 (referent)<br>– Current: 1.31 (1.13–1.52) |

**Table 6.8*S* Continued**

| Study | Design/population | Findings by measure of smoking | |
|---|---|---|---|
| | | **Incidence: RR (95% CI)** | **Mortality: RR (95% CI)** |
| Engeland et al. 1996 | • British-Norwegian Migrant Study<br>• 11,863 men<br>• 707 cases<br>• 1966–1993 | • Adjusted for age<br>• Smoking status:<br>– Never smoker: 1.0 (referent)<br>– Former smoker: 0.9 (0.7–1.1)<br>– Current smoker: 1.1 (0.9–1.3) | • NR |
| Grönberg et al. 1996 | • Nested case-control study<br>• Swedish male twins born between 1886–1925<br>• 470 cases<br>• 1959–1989 | • Adjusted for age<br>• Smoking status:<br>– Never smoker: 1.00 (referent)<br>– Former smoker: 0.91 (0.68–1.21)<br>– Current smoker: 1.00 (0.71–1.39)<br>– p trend = 0.91<br>• Number of cigarettes/day:<br>– 0: 1.00 (referent)<br>– 1–9: 1.06 (0.77–1.45)<br>– 10–19: 0.96 (0.66–1.39)<br>– ≥20: 0.72 (0.43–1.15)<br>– p trend = 0.18 | • NR |

**Table 6.8*S* Continued**

| Study | Design/population | Findings by measure of smoking | |
|---|---|---|---|
| | | **Incidence: RR (95% CI)** | **Mortality: RR (95% CI)** |
| Cerhan et al. 1997 | • Iowa 65+ Rural Health Study (1 of the sites in the EPESE)<br>• 1,050 men, ≥65 years of age<br>• 71 cases<br>• 1982–1993 | • Adjusted for age<br>• Smoking status:<br>– Never smoker: 1.0 (referent)<br>– Former smoker: 1.2 (0.7–2.1)<br>– Current smoker: 2.2 (1.2–4.4)<br>– p trend = 0.02<br>• Pack-years of smoking:<br>– 0: 1.0 (referent)<br>– <31: 1.3 (0.7–2.5)<br>– 31–55: 1.3 (0.7–2.7)<br>– >55: 2.0 (1.1–3.8)<br>– p trend = 0.04<br>• Number of cigarettes/day by smoking status (for current only):<br>– Never smoker: 1.0 (referent)<br>– Former smoker: 1.2 (0.7–2.1)<br>– Current smoker, <20: 1.8 (0.7–4.4)<br>– Current smoker, ≥20: 2.7 (1.2–6.0)<br>– p trend = 0.007<br>• Years since quitting smoking by smoking status:<br>– Never smoker: 1.0 (referent)<br>– Former smoker, quit ≥15 years ago: 1.3 (0.7–2.5)<br>– Former smoker, quit <15 years ago: 1.1 (0.6–2.2)<br>– Current smoker: 2.2 (1.2–4.4)<br>– p trend = 0.03 | NR |

**Table 6.8*S* Continued**

| Study | Design/population | Findings by measure of smoking | |
|---|---|---|---|
| | | **Incidence: RR (95% CI)** | **Mortality: RR (95% CI)** |
| Rodriguez et al. 1997 | • CPS-II of the American Cancer Society<br>• 450,279 men<br>• 1,748 deaths<br>• 1982–1991<br>• United States | • NR | • Adjusted for multiple variables<br>• Smoking status (former smoker):<br>– Never smoker: 1.00 (referent)<br>– Cigarettes only: 0.99 (0.87–1.12)<br>– Pipe/cigars/cigarettes: 0.91 (0.78–1.08)<br>• Smoking status (current smoker):<br>– Never smoker: 1.00 (referent)<br>– Cigarettes only: 1.34 (1.16–1.56)<br>– Pipe/cigars/cigarettes: 0.87 (0.73–1.05)<br>• Number of cigarettes/day (current smoker):<br>– Never smoker: 1.00 (referent)<br>– <10: 1.33 (0.96–1.83)<br>– ≥10–<20: 1.58 (1.23–2.03)<br>– 20: 1.38 (1.10–1.71)<br>– >20: 1.25 (1.00–1.57)<br>– p trend = 0.29<br>• Smoking duration (years) (current smoker):<br>– Never smoker: 1.00 (referent)<br>– ≤25: 1.36 (0.77–2.38)<br>– >25–35: 1.65 (1.17–2.34)<br>– >35–45: 1.39 (1.11–1.75)<br>– >45: 1.26 (1.04–1.53)<br>– p trend = 0.86 |
| Tulinius et al. 1997 | • Cardiovascular Risk Factor Study (also known as the Reykjavik Study)<br>• 11,366 men<br>• 524 cases<br>• 1968–1995<br>• Iceland | • Adjusted for age<br>• Smoking status:<br>– Never smoker: 1.00 (referent)<br>– Former smoker: NR<br>– Current smoker: NR<br>• Number of cigarettes/day:<br>– 1–14: NR<br>– 15–24: NR<br>– ≥25: NR<br>– p ≥ 0.10 for all categories versus never smoking | NR |

**Table 6.8*S* Continued**

| Study | Design/population | Findings by measure of smoking | |
|---|---|---|---|
| | | **Incidence: RR (95% CI)** | **Mortality: RR (95% CI)** |
| Veierød et al. 1997 | • 24,051 Norwegian males, 16–56 years of age, who underwent screening for cardiovascular disease<br>• 69 cases<br>• 1977–1992 | • Adjusted for age<br>• Number of cigarettes/day by smoking status (for current only):<br>– Never smoker: 1.0 (referent)<br>– Former smoker: 0.6 (0.3–1.1)<br>– Current smoker: 0–10: 0.5 (0.3–1.1)<br>– Current smoker: ≥11: 0.6 (0.3–1.2) | NR |
| Lotufo et al. 2000 | • Physicians' Health Study<br>• 22,071 men, 40–84 years of age<br>• 1982–2000<br>• 996 cases<br>• 113 deaths<br>• United States | • Adjusted for multiple variables<br>• Smoking status:<br>– Never smoker: 1.00 (referent)<br>– Former smoker: 1.11 (0.98–1.28)<br>– Current smoker, <20 cigarettes/day: 1.04 (0.73–1.48)<br>– Current smoker, ≥20 cigarettes/day: 1.07 (0.82–1.41)<br>– p trend = 0.33<br>• Pack-years of smoking:<br>– Never smoker: 1.00 (referent)<br>– 0.25–19: 1.20 (1.02–1.41)<br>– 20–39: 0.96 (0.78–1.17)<br>– ≥40: 1.14 (0.93–1.40)<br>– p trend = 0.38<br>• Smoking duration (years) among current smokers:<br>– <29: 1.00 (referent)<br>– 29–38: 1.69 (0.75–3.82)<br>– ≥39: 1.05 (0.41–2.70)<br>– p trend = 0.33 | • Adjusted for multiple variables<br>• Smoking status:<br>– Never smoker: 1.00 (referent)<br>– Former smoker: 1.30 (0.87–1.95)<br>– Current smoker:<br>– <20 cigarettes/day: 1.25 (0.45–3.49)<br>– ≥20 cigarettes/day: 1.22 (0.54–2.74)<br>– p trend = 0.38<br>• Pack-years of smoking:<br>– Never smoker: 1.00 (referent)<br>– 0.25–19: 1.35 (0.82–2.23)<br>– 20–39: 1.14 (0.64–2.05)<br>– ≥40: 0.91 (0.47–1.75)<br>– p trend = 0.98 |

**Table 6.8*S* Continued**

| Study | Design/population | Findings by measure of smoking | |
|---|---|---|---|
| | | **Incidence: RR (95% CI)** | **Mortality: RR (95% CI)** |
| Lund Nilsen et al. 2000 | • 22,895 men, ≥20 years of age, who participated in the National Health Screening Service from 1984–1986<br>• 1984–1996<br>• 644 cases<br>• Nord-Trondelag, Norway | • Adjusted for age<br>• Smoking status:<br>– Never smoker: 1.00 (referent)<br>– Former smoker: 0.98 (0.80–1.19)<br>– Current smoker: 0.96 (0.78–1.19)<br>– p trend = 0.69<br>• Number of cigarettes/day:<br>– 0: 1.00 (referent)<br>– 1–8: 0.84 (0.64–1.10)<br>– 9–10: 1.05 (0.79–1.39)<br>– 11–15: 1.37 (1.00–1.88)<br>– >15: 1.27 (0.91–1.76)<br>• Pack-years of smoking:<br>– 0: 1.00 (referent)<br>– 1–10: 0.95 (0.70–1.30)<br>– 11–17: 0.84 (0.58–1.21)<br>– 18–25: 1.24 (0.92–1.67)<br>– >25: 1.22 (0.93–1.60) | NR |
| Putnam et al. 2000[d] | • 1,572 men (controls) who participated in a population-based case-control study of cancer from 1986–1989<br>• 101 cases<br>• 1986–1995<br>• Iowa | • Adjusted for age<br>• Smoking status:<br>– Never smoker: 1.0 (referent)<br>– Former smoker: 1.4 (0.9–2.3)<br>– Current smoker, <20 cigarettes/day: 1.3 (0.6–2.8)<br>– Current smoker, ≥20 cigarettes/day: 1.6 (0.7–3.9)<br>– p trend = 0.2<br>• Pack-years of smoking:<br>– Never smoker: 1.0 (referent)<br>– <25: 1.7 (1.0–3.0)<br>– 25–50: 1.2 (0.7–2.2)<br>– >50: 1.4 (0.8–2.5)<br>– p trend = 0.5 | NR |
| Allen et al. 2004 | • Life Span Study<br>• 18,115 Japanese men who were residents of Nagasaki and Hiroshima at the time of the atomic bombings during World War II<br>• 196 cases<br>• 1963–1996 | • Adjusted for age, year, city, radiation dose, and education<br>• Smoking status:<br>– Nonsmoker: 1.00 (referent)<br>– Smoker: 0.80 (0.60–1.07) | NR |

**Table 6.8*S* Continued**

| Study | Design/population | Findings by measure of smoking | |
|---|---|---|---|
| | | **Incidence: RR (95% CI)** | **Mortality: RR (95% CI)** |
| Doll et al. 2005[e] | • British Doctors Study<br>• 34,439 male physicians<br>• 878 deaths<br>• 1951–2001 | NR | • Prostate cancer mortality rate adjusted for age and year<br>• Smoking status:<br>– Never smoker: 89.4/100,000 men/year<br>– Former smoker: 80.9/100,000 men/year<br>– Current smoker: 90.0/100,000 men/year<br>– p trend = 0.67<br>• Number of cigarettes/day among current smokers:<br>– 1–14: 66.7/100,000 men/year<br>– 15–24: 99.6/100,000 men/year<br>– ≥25: 113.3/100,000 men/year<br>– p trend = 0.52 |
| Giovannucci et al. 2007[f] | • Health Professionals Follow-Up Study<br>• 51,529 men, 40–75 years of age<br>• 3,544 cases<br>• 312 deaths<br>• 1986–2002<br>• United States | • Adjusted for multiple variables<br>• Smoking status:<br>– Never smoker: 1.0 (referent)<br>– Former smoker, quit >10 years ago: 0.98<br>– Current or former smoker, quit ≤10 years ago: 0.98 (0.89–1.07)<br>– p trend = 0.53<br>• Organ-confined disease by smoking status:<br>– Never smoker: 1.00 (referent)<br>– Current or former smoker, quit ≤10 years ago: 0.88 (0.77–1.01)<br>• Minimally extraprostatic disease by smoking status:<br>– Never smoker: 1.00 (referent)<br>– Current or former smoker, quit ≤10 years ago: 1.11 (0.82–1.52)<br>• Advanced-stage disease by smoking status:<br>– Never smoker: 1.00 (referent)<br>– Current or former smoker, quit ≤10 years ago: 1.14 (0.90–1.45) | • Adjusted for multiple variables<br>• Smoking status:<br>– Never smoker: 1.00 (referent)<br>– Former smoker, quit >10 years ago: 1.03<br>– Current or former smoker, quit ≤10 years ago: 1.41 (1.04–1.91)<br>– p trend = 0.05 |

**Table 6.8*S* Continued**

| Study | Design/population | Findings by measure of smoking | |
|---|---|---|---|
| | | **Incidence: RR (95% CI)** | **Mortality: RR (95% CI)** |
| Rohrmann et al. 2007 | • 26,810 men, ≥18 years of age, who responded to a private census<br>• 1963–2000<br>• 147 cases<br>• 240 deaths<br>• Washington County, Maryland | • 1963 cohort adjusted for age<br>• Smoking status:<br>– Never smoker: 1.00 (referent)<br>– Former smoker: 1.33 (0.85–2.10)<br>– Current smoker: 1.00 (0.63–1.59)<br>• Number of cigarettes/day among current smokers:<br>– Never smoker: 1.00 (referent)<br>– <10: 0.52 (0.20–1.33)<br>– 10–19: 1.03 (0.60–1.79)<br>– ≥20: 1.38 (0.75–2.54)<br>• First 10 years of follow-up, by smoking status:<br>– Never smoker: 1.00 (referent)<br>– Former smoker: 1.44 (0.89–2.32)<br>– Current smoker: 0.90 (0.54–1.51) | • 1963 cohort adjusted for age<br>• Smoking status:<br>– Never smoker: 1.00 (referent)<br>– Former smoker: 1.01 (0.70–1.46)<br>– Current smoker: 0.93 (0.67–1.29)<br>• Number of cigarettes/day among current smokers:<br>– Never smoker: 1.00 (referent)<br>– <10: 1.11 (0.67–1.29)<br>– 10–19: 0.85 (0.57–1.25)<br>– ≥20: 0.95 (0.62–1.47)<br>• First 10 years of follow-up, by smoking status:<br>– Never smoker: 1.00 (referent)<br>– Former smoker: 2.75 (1.13–6.74)<br>– Current smoker: 2.38 (0.94–5.99) |
| Rohrmann et al. 2007 | • 28,292 adult men<br>• 351 cases<br>• 184 deaths<br>• 1975–2000 | • 1975 cohort<br>• Smoking status:<br>– Never smoker: 1.00 (referent)<br>– Former smoker: 1.04 (0.80–1.36)<br>– Current smoker: 0.98 (0.73–1.33)<br>• Number of cigarettes/day among current smokers:<br>– Never smoker: 1.00 (referent)<br>– <10: 1.12 (0.58–2.15)<br>– 10–19: 0.95 (0.67–1.35)<br>– ≥20: 1.01 (0.65–1.57)<br>• First 10 years of follow-up by smoking status:<br>– Never smoker: 1.00 (referent)<br>– Former smoker: 1.03 (0.76–1.40)<br>– Current smoker: 1.08 (0.76–1.53) | • 1975 cohort<br>• Smoking status:<br>– Never smoker: 1.00 (referent)<br>– Former smoker: 1.02 (0.69–1.50)<br>– Current smoker: 1.25 (0.84–1.87)<br>• Number of cigarettes/day among current smokers:<br>– Never smoker: 1.00 (referent)<br>– <10: 1.12 (0.44–2.82)<br>– 10–19: 1.11 (0.70–1.77)<br>– ≥20: 1.58 (0.94–2.64)<br>• First 10 years of follow-up by smoking status:<br>– Never smoker:1.00 (referent)<br>– Former smoker: 1.92 (0.67–5.49)<br>– Current smoker: 2.21 (0.69–7.08) |

**Table 6.8*S* Continued**

| Study | Design/population | Findings by measure of smoking | |
|---|---|---|---|
| | | **Incidence: RR (95% CI)** | **Mortality: RR (95% CI)** |
| Batty et al. 2008 | • Whitehall Study<br>• 17,363 men, 40–69 years of age, who were government employees<br>• 484 deaths<br>• 1967–2005<br>• London | NR | • Adjusted for multiple variables<br>• Smoking status:<br>– Never smoker: 1.00 (referent)<br>– Former smoker: 1.10 (0.86–1.41)<br>– Current: 1.30 (1.01–1.69)<br>– p trend = 0.03<br>• Per 10 cigarettes/day:<br>– Former smoker: 0.97 (0.85–1.11)<br>– Current smoker: 1.12 (0.96–1.31)<br>• Per 10 years of smoking:<br>– Former smoker: 1.05 (0.93–1.20)<br>– Current smoker: 0.93 (0.75–1.15) |
| Watters et al. 2009 | • NIH-AARP Diet and Health Study<br>• 283,312 men 50–71 years of age<br>• 14,/810 cases<br>• 394 deaths<br>• 1995–2003<br>• United States | • Adjusted for multiple variables<br>• Smoking status:<br>– Never smoker: 1.00 (referent)<br>– Former smoker: 0.90 (0.87–0.93)<br>– Current smoker: 0.85 (0.80–0.90)<br>– p trend <0.001<br>• Number of cigarettes/day:<br>– Never smoker: 1.00 (referent)<br>– 1–10: 0.93 (0.89–0.98)<br>– 11–20: 0.90 (0.87–0.94)<br>– 21–30: 0.88 (0.84–0.93)<br>– 31–40: 0.86 (0.81–0.91)<br>– 41–60: 0.87 (0.82–0.94)<br>– >60: 0.79 (0.68–0.89)<br>– p trend <0.001<br>• Dose by smoking status:<br>– Never smoker: 1.00 (referent)<br>– Former smoker, ≤1 pack/day: 0.92 (0.88–0.95)<br>– Former smoker, >1 pack/day: 0.88 (0.85–0.92)<br>– Current smoker, ≤1 pack/day: 0.91 (0.84–0.97)<br>– Current smoker, >1 pack/day: 0.75 (0.69–0.83)<br>– p trend <0.001 | • Adjusted for multiple variables<br>• Smoking status:<br>– Never smoker: 1.00 (referent)<br>– Former smoker:1.03 (0.83–1.27)<br>– Current smoker: 1.69 (1.25–2.27)<br>– p trend = 0.005<br>• Number of cigarettes/day:<br>– Never smoker: 1.00 (referent)<br>– 1–10: 1.07 (0.80–1.45)<br>– 11–20: 1.11 (0.86–1.44)<br>– 21–30: 1.10 (0.82–1.47)<br>– 31–40: 1.31 (0.96–1.79)<br>– 41–60: 0.96 (0.64–1.44)<br>– >60: 1.09 (0.57–2.09)<br>– p trend = 0.40<br>• Dose by smoking status:<br>– Never smoker: 1.00 (referent)<br>– Former smoker, ≤1 pack/day: 0.97 (0.76–1.24)<br>– Former smoker, >1 pack/day: 1.09 (0.85–1.39)<br>– Current smoker, ≤1 pack/day: 1.79 (1.27–2.52)<br>– Current smoker, >1 pack/day: 1.54 (1.01–2.34)<br>– p trend = 0.02 |

**Table 6.8*S* Continued**

| Study | Design/population | Findings by measure of smoking | |
|---|---|---|---|
| | | **Incidence: RR (95% CI)** | **Mortality: RR (95% CI)** |
| Weinmann et al. 2010 | • Prostate Cancer Sceening and Mortality Study<br>• Nested case-control<br>• Men who were members of one of several health plans<br>• 768 deaths<br>• 1997–2001<br>• United States | NR | • Adjusted for age, race, health plan, and reference date<br>• Smoking status:<br>– Never: 1.0 (referent)<br>– Former: 1.0 (0.81–1.3)<br>– Current: 1.5 (1.1–2.0)<br>• History of tobacco use (any type) by smoking status:<br>– Never smoker: 1.0 (referent)<br>– Former smoker: 1.1 (0.89–1.4)<br>– Current smoker: 1.7 (1.2–2.3) |

*Note:* **CI** = confidence interval; **CPS** = Cancer Prevention Study; **EPESE** = Established Populations for Epidemiologic Studies of the Elderly; **g** = grams; **NIH** = National Institutes of Health; **NR** = not reported; **RR** = relative risk.

[a]Excluded two prospective studies that did not report on rates, risks, or RRs (odds ratio): Heikkilä and colleagues (1999) and Eichholzer and colleagues (1999).

[b]Update of Hirayama (1979).

[c]Update of Dorn (1959), Kahn (1966), and Rogot and Murray (1980), and same data as in McLaughlin and colleagues (1995).

[d]Update of Parker and colleagues (1999).

[e]Update of Doll and Hill (1966), Doll and Peto (1976), and Doll and colleagues (1994).

[f]Update of Giovannucci and colleagues (1999).

**Table 6.9*S*** **Epidemiologic cross-sectional studies on the association between cigarette smoking and stage and histologic grade at diagnosis of prostate cancer**

| Study | Design/population | Findings by measure of smoking: OR (95% CI) |
|---|---|---|
| Hussain et al. 1992 | • Cases treated with external beam radiation and surgery at 1 hospital<br>• 670 cases<br>• Dates of diagnoses: 1980–1990 | • Disease stage among nonsmokers:[a]<br>– Stage A: 4.4%<br>– Stage B: 35.6%<br>– Stage C: 6.7%<br>– Stage D: 53.3%<br>• Disease stage among smokers:[a]<br>– Stage A: 4.4%<br>– Stage B: 17.4%<br>– Stage C: 9.9%<br>– Stage D: 68.3%<br>• Histologic grade among nonsmokers:[b]<br>– Well differentiated: 37.1%<br>– Moderately differentiated : 45.2%<br>– Poorly differentiated: 17.7%<br>• Histologic grade among smokers:[b]<br>– Well differentiated: 15.0%<br>– Moderately differentiated: 27.1%<br>– Poorly differentiated: 57.9% |
| Daniell 1995 | • Cases seen at 1 community hospital<br>• 359 cases<br>• Dates of diagnoses: 1983–1990 | • Disease Stage D vs. nonstage A, by smoking status:<br>– Nonsmoker: 1.0 (referent)<br>– Smoker: 2.1 (1.3–4.3)[c] |
| Kobrinsky et al. 2003 | • Cases recorded in a regional cancer registry<br>• 2,311 cases<br>• Dates of diagnoses: 1986–2001 | • Metastatic (SEER cancer stage 7) by smoking status:<br>– Never smoker: 1.00 (referent)<br>– Former smoker: 0.94 (0.72–1.21)<br>– Current smoker: 1.53 (1.17–2.02)<br>• Regional (SEER cancer stages 3, 4, 5) by smoking status:<br>– Never smoker: 1.00 (referent)<br>– Former smoker: 1.01 (0.63–1.63)<br>– Current smoker: 1.83 (1.09–3.06) |

**Table 6.9*S* Continued**

| Study | Design/population | Findings by measure of smoking: OR (95% CI) |
|---|---|---|
| Roberts et al. 2003 | • Clinically localized cases treated with surgery by 1 surgeon<br>• Diagnosed between 1992–1999<br>• 352 cases | • Gleason score ≥7 vs. <7, by smoking status:<br>– Never smoker: 1.00 (referent)<br>– Former smoker: 0.72 (0.44–1.19)<br>– Current smoker: 1.76 (0.66–4.72)<br>• Extraprostatic disease vs. not, by smoking status:<br>– Never smoker: 1.00 (referent)<br>– Former smoker: 1.49 (0.92–2.42)<br>– Current smoker: 3.85 (1.44–10.33)<br>• Gleason score ≥7 or extraprostatic vs. not, by smoking status:<br>– Never smoker: 1.00 (referent)<br>– Former smoker: 1.47 (0.84–2.56)<br>– Current smoker: 3.17 (1.13–8.85)<br>• Gleason score ≥7 vs. <7, by pack-years of smoking:<br>– Never smoker: 1.00 (referent)<br>– ≤10: 0.57 (0.31–1.06)<br>– >10–20: 1.03 (0.45–2.38)<br>– >20–30: 0.68 (0.26–1.76)<br>– >30–40: 1.76 (0.52–5.97)<br>– >40: 2.01 (0.65–6.24)<br>– p trend = 0.16<br>• Extraprostatic disease vs. not, by pack-years of smoking:<br>– Never smoker: 1.00 (referent)<br>– ≤10: 1.23 (0.69–2.18)<br>– >10–20: 2.29 (1.03–5.10)<br>– >20–30: 1.45 (0.60–3.51)<br>– >30–40: 3.01 (0.90–10.03)<br>– >40: 3.66 (1.18–22.29)<br>– p trend = 0.005<br>• Gleason score ≥7 or extraprostatic vs. not, by pack-years of smoking:<br>– Never smoker: 1.00 (referent)<br>– ≤10: 1.05 (0.53–2.07)<br>– >10–20: 2.03 (0.84–4.91)<br>– >20–30: 1.82 (0.71–4.66)<br>– >30–40: 3.84 (1.07–13.73)<br>– >40: 3.37 (1.04–10.98)<br>– p trend = 0.003 |

**Table 6.9*S* Continued**

| Study | Design/population | Findings by measure of smoking: OR (95% CI) |
|---|---|---|
| Moreira et al. 2010 | • Localized cases treated with surgery<br>• 1,267 cases<br>• Dates of diagnoses: 1998–2008 | • Gleason score among current smokers at prostatectomy:[d]<br>– 2–6 : 35%<br>– 3+4: 44%<br>– ≥4+3: 21%<br>• Gleason score among nonsmokers at prostatectomy:[d]<br>– 2–6: 41%<br>– 3+4: 39%<br>– ≥4+3: 20%<br>• Extraprostatic extension by smoking status at prostatectomy:<br>– Smoker: 25%<br>– Nonsmoker: 18%<br>– p = 0.003<br>• Invasion of seminal vesicles by smoking status at prostatectomy:<br>– Smoker: 10%<br>– Nonsmoker: 6%<br>– p = 0.03<br>• Lymph-node positive by smoking status at prostatectomy:<br>– Smoker: 2%<br>– Nonsmoker: 2%<br>– p = 0.52 (out of those with known lymph node status) |

*Note:* **CI** = confidence interval; **OR** = odds ratio; **pack-years** = the number of years of smoking multiplied by the number of packs of cigarettes smoked per day; **SEER** = Surveillance, Epidemiology, and End Results Program. Gleason sum is the sum of the 2 scores given by the pathologist on examination of the prostatic tissue.
[a]Distribution of stage by smoking status; p = 0.01.
[b]Distribution of grade by smoking status; p <0.00005.
[c]Results adjusted for multiple variables, including grade.
[d]Distribution by smoking status: p = 0.15.

**Table 6.10*S* Cohort studies on the association between cigarette smoking and risk of prostate cancer progression, case fatality, and all-cause mortality in men with prostate cancer**

| Study | Design/population | Number of progressors, prostate cancer deaths, or deaths from all causes | Findings by smoking status: RR (95% CI)[a] | | |
|---|---|---|---|---|---|
| | | | Progression | Case fatality (prostate cancer-specific mortality) | All-cause mortality (unless otherwise noted) |
| Daniell 1995 | • Retrospective study<br>• 359 cases; 235 nonstage A, of which 46 were stage D2<br>• Dates of diagnoses: 1983–1990 | 57 prostate cancer deaths (30 were among men with stage D2) | NR | • 5-year cumulative incidence in nonstage A cases:<br>– Nonsmoker: 17%<br>– Smoker: 39%<br>– p <0.001<br>• 5-year cumulative incidence in stage D2 cases:<br>– Nonsmoker: 63%<br>– Smoker: 88%<br>– p <0.05 | NR |
| Yu et al. 1997[b] | • Retrospective study<br>• 1,820 cases: 1,079 local; 463 regional; 207 distant: 1,695 Whites; 94 Blacks<br>• Dates of diagnoses: 1990–1995 | Deaths from all causes: NR | NR | NR | • Nondrinkers:<br>– Never smokers: 1.00 (referent)<br>– Ever smokers: 1.98 (1.1–3.7)<br>• White:<br>– Never smokers: 1.00 (referent)<br>– Ever smokers: 1.53 (1.0–2.2)<br>• Black:<br>– Never smokers: 1.00 (referent)<br>– Ever smokers: 0.89 (0.1–6.7)<br>• Local:<br>– Never smokers: 1.00 (referent)<br>– Ever smokers: 0.77 (0.4–1.5)<br>• Regional:<br>– Never smokers: 1.00 (referent)<br>– Ever smokers: 3.07 (1.2–7.9)<br>• Distant:<br>– Never smokers: 1.00 (referent)<br>– Ever smokers: 1.29 (0.7–2.3)<br>• Pack-years of smoking:<br>– Never smokers: 1.00 (referent)<br>– 1–59: 1.42<br>– ≥60: 2.65<br>– p trend = 0.00 |

**Table 6.10*S* Continued**

| Study | Design/population | Number of progressors, prostate cancer deaths, or deaths from all causes | Findings by smoking status: RR (95% CI)[a] | | |
|---|---|---|---|---|---|
| | | | Progression | Case fatality (prostate cancer-specific mortality) | All-cause mortality (unless otherwise noted) |
| Merrick et al. 2004[c] | • Retrospective study<br>• 582 localized cases treated with brachytherapy<br>• Dates of diagnoses: 1995–2000<br>• Follow-up (median): 54.5 months | 27 cases (biochemical progression or death from prostate cancer)<br>38 deaths (6 due to prostate cancer) | • Smoking status:<br>– Never: 1.00 (referent)<br>– Former: 1.31 (p = 0.586)<br>– Current: 2.69 (p = 0.067)[d] | NR | NR |
| Oefelein and Resnick 2004[e] | • Retrospective study<br>• 222 advanced-stage cases treated with hormone deprivation therapy<br>• Dates of diagnoses: 1987–2003<br>• Follow-up (median): 141 months | 133 Progressors (development of hormone-refractory prostate cancer)<br>77 Deaths (61 prostate cancer) | • Per pack-year of smoking: 3.0; p trend = 0.003<br>• Recent tobacco use: 2.7; p = 0.007 | NR | • Per pack-year of smoking: 5.3; p trend = 0.0001<br>• Recent tobacco use: NR; p = 0.06 |
| Pickles et al. 2004[c] | • Retrospective study<br>• 601 localized cases treated with external beam radiation<br>• Dates of diagnoses: 1994–1997<br>• Follow-up (median): 59 months | Progressors: NR<br>Deaths: N | • Smoking status [OR (95% CI)]:<br>– Never: 1.00 (referent)<br>– Current: 1.68 (1.11–2.56)<br>• Current vs. former: NR<br>– p = 0.3 | • 6-year cumulative incidence of death:<br>– Never smokers: 3.7%<br>– Current smokers: 10%<br>– p = 0.08 | • 6-year cumulative incidence of death:<br>– Never smokers: 10.8%<br>– Current smokers: 25.7%<br>– p = 0.009 |
| Jager et al. 2007 | • Retrospective study<br>• 214 cases across stages: local: ~50%; regional: ~40%; distant: ~10%<br>• Dates of diagnoses: 1991–2001<br>• Follow-up (median): 50 months | 47 prostate cancer deaths | NR | • 10-year survival rate:<br>– Nonsmoker: 87%<br>– Current smoker: 58%<br>– p <0.02<br>• Smoking status:<br>– Nonsmoker: 1.0 (referent)<br>• Current smoker: 3 | • 90-month survival rate:<br>– Nonsmoker: 93%<br>– Current smoker: 79% |

**Table 6.10*S* Continued**

| Study | Design/population | Number of progressors, prostate cancer deaths, or deaths from all causes | Findings by smoking status: RR (95% CI)[a] | | |
|---|---|---|---|---|---|
| | | | Progression | Case fatality (prostate cancer-specific mortality) | All-cause mortality (unless otherwise noted) |
| Pantarotto et al. 2007[c] | • Retrospective study<br>• 416 cases of clinical stage T1–T4 N0M0 (nodes 0, metastases 0) prostate cancer treated with external beam radiotherapy<br>• Dates of diagnoses: 1990–1999<br>• Follow-up (median): 70.3 months | Cases (calculated from Table 6.8*S*): 97 local recurrence; 185 biochemical failure; 64 distant failure and 58 prostate cancer-specific deaths | • Biochemical failure:<br>– Never smoker: 1.00 (referent)<br>– Former smoker: 1.14 (p = 0.51)<br>– Current smoker: 1.49 (0.88–2.40)<br>– p = 0.12<br>• Local recurrence:<br>– Never smoker: 1.00 (referent)<br>– Former smoker: 1.10 (p = 0.71)<br>– Current smoker: 0.96<br>– p = 0.91<br>• Distant failure:<br>– Never smoker: 1.00 (referent)<br>– Former smoker: 2.90 (1.09–7.67; p = 0.03)<br>– Currrent smoker: 5.24 (1.75–15.7)<br>– p = 0.003 | • Never smoker: 1.00 (referent)<br>• Former smoker: 1.78; p = 0.18<br>• Current smoker: 1.39; p = 0.55 | • Never smoker: 1.00 (referent)<br>• Former smoker: 1.51; p = 0.11<br>• Current smoker: 1.72 (0.94–3.15); p = 0.08 |

**Table 6.10*S* Continued**

| Study | Design/population | Number of progressors, prostate cancer deaths, or deaths from all causes | Findings by smoking status: RR (95% CI)[a] | | |
|---|---|---|---|---|---|
| | | | Progression | Case fatality (prostate cancer-specific mortality) | All-cause mortality (unless otherwise noted) |
| Gong et al. 2008[c] | • Prospective study<br>• 752 cases across stages: local: 552; regional: 175; distant: 25<br>• Dates of diagnoses: 1993–1996<br>• Follow-up (median): 11.5 years | 135 all-cause deaths (54 prostate cancer) | NR | • Smoking status:<br>– Never smoker: 1.00 (referent)<br>– Quit ≥10 years ago: 0.45 (0.19–1.05)<br>– Quit <10 years ago: 1.48 (0.50–4.37)<br>– Current smoker: 2.66 (1.10–6.43)<br>• Pack-years of smoking within 10 years of diagnosis:<br>– 0: 1.00 (referent)<br>– 1–9: 2.70 (1.10–6.64<br>– 10–14: 2.95 (1.08–8.07)<br>– ≥15: 5.82 (1.96–17.26)<br>– p trend = 0.0002 | • Death from all other causes by smoking status:<br>– Never smoker: 1.00 (referent)<br>– Quit ≥10 years ago: 1.29 (0.70–2.38)<br>– Quit <10 years ago: 1.69 (0.81–3.56)<br>– Current smoker: 2.42 (1.24–4.72)<br>• Pack-years of smoking within 10 years of diagnosis:<br>– 0: 1.00 (referent)<br>– 1–9: 1.32 (0.66–2.63)<br>– 10–14: 2.29 (1.26–4.16)<br>– ≥15: 1.87 (0.81–4.33)<br>– p trend = 0.01 |
| Moreira et al. 2010[f] | • Retrospective study<br>• 1,267 cases across stages: 254 extracapsular extension; 92 invasion of seminal vesicles; 17 lymph node positive (the 3 categories are not mutually exclusive)<br>• Dates of diagnoses: 1998–2008<br>• Follow-up (median): 3.1 years | Biochemical recurrence: NR | • Smoking status at prostatectomy:<br>– Nonsmoker: 1.00 (referent)<br>– Smoker: 0.91 (0.70–1.18) | NR | NR |

*Note:* **CI** = confidence interval; **NR** = not reported; **OR** = odds ratio; **pack-years** = the number of years of smoking multiplied by the number of packs of cigarettes smoked per day; **RR** = relative risk.
[a]Results are reported by relative risk unless noted otherwise.
[b]Results are adjusted for multiple variables, including grade.
[c]Results are adjusted for multiple variables, including stage and grade.
[d]Table 3*S* in the report by Merrick and colleagues (2004) appears to have erroneous labels for the comparisons made.
[e]Results are adjusted for multiple variables, including stage.
[f]Results are adjusted for multiple variables, including pathologic stage and grade.

**Table 6.11*S* Reports on levels of endogenous hormones and smoking in premenopausal women (n = 22)**

| Study | Population | Sample/period | Definition of smoking (number of subjects) | Findings among smokers: Estimate of effect (95% CI or p value) | Comments |
|---|---|---|---|---|---|
| MacMahon et al. 1982 | • 106 White women<br>• 25–49 years of age | Overnight urine specimen<br>FP (days 10–11)<br>LP (days 21–22) | Nonsmoker (n = 44): ≤100 cigarettes smoked during lifetime<br>Former smoker (n = 23)<br>Current smoker (n = 39) | • Levels of E1, E2, and E3 in smokers were similar to nonsmokers during FP<br>• Total levels of E1, E2, and E3 decreased 29% (10–43) during LP<br>• Little difference in former smokers | Stronger effects during ovulatory cycles; adjusted for age |
| Michnovicz et al. 1986 | • 27 nonobese women with normal-length menstrual cycle<br>• Age (mean): approximately 30 years | Blood and urine samples over 48 hours after administration of radiolabeled E2<br>FP (days 1–10), in morning<br>5 samples during LP (days 19–25) | Smoker (n = 14): ≥15 cigarettes/day | • 2-hydroxylation increased 50% ($p < 0.001$)<br>• Urine E3 and E3/E1 decreased 40% ($p < 0.01$) | No difference during FP vs. LP; age and BMI were similar in nonsmokers and smokers, so no adjustments were made |
| Ernster et al. 1987 | • 562 women | Breast fluid by nipple aspiration and blood sample | Current, former, and never smoker | • E2 hydroxylation increased 50% ($p < 0.001$)<br>• 2OHE1 increased ($p < 0.02$). E3 decreased ($p < 0.05$)<br>• No difference in 16αOHE1, E2, E1, and total estrogens | No adjustments were made for BMI, age, etc. |
| Michnovicz et al. 1988 | • 29 nonobese women<br>• 21–44 years of age | Urine samples over 48 hours after administration of radiolabeled E2<br>Mid-FP (days 1–12) | Smoker (n = 15): 15–30 cigarettes/day<br>Cotinine not detected in nonsmokers | • E1 increased per pack-year of smoking ($p = 0.05$) | Adjusted for previous thyroid disease |
| Longcope and Johnston 1988 | • 88 women (47 premenopausal)<br>• Age (mean): 50 years | Radiolabeled steroid infusion<br>Blood and urine samples at baseline | Smoker (n = 23): 10 cigarettes/day for ≥10 years | • Metabolic clearance rates decreased for testosterone, androstenedione, and E1 were not significant in premenopausal women ($p < 0.05$)<br>• Increased plasma androstenedione ($p < 0.02$)<br>• No difference in E1 and E2<br>• No difference in SHBG, steroid production rates, and aromatization of androgens | No difference after adjusting for weight; no interaction between menopausal status and smoking for any of variables |

**Table 6.11*S* Continued**

| Study | Population | Sample/period | Definition of smoking (number of subjects) | Findings among smokers: Estimate of effect (95% CI or p value) | Comments |
|---|---|---|---|---|---|
| Zumoff et al. 1990 | • 16 volunteers with normal ovulatory and luteal function<br>• 25–35 years of age | Blood samples on 17 days over cycle, and more frequently around mid-cycle (ovulation) | Smoker (n = 8): ≥20 cig/ per day for ≥3 years | • Progesterone increased 37% during FP but not LP (p <0.0001)<br>• E2 increased 23% during early FP (p <0.001) and 12.5% (p = approximately 0.05) through FP, but results were not significant<br>• Slightly decreased mean LH | Smoking may stimulate adrenocortical hormone secretion |
| Key et al. 1991 | • Women recruited from Guernsey Breast Cancer Study with menstrual cycle lengths of 21–35 days<br>• Serum E2 and progesterone (n = 147)<br>• Serum DHEA-S (n = 411)<br>• Urinary steroids (n = 105)<br>• ≥35 years of age | 24-hour urine sample and 1 blood sample | Current smoker: 1–10, 11–20, and ≥21 cigarettes/ day<br>E2 and progesterone (n = 69)<br>DHEA-S (n = 97)<br>Urinary steroids (n = 20) | • No difference in serum E2, progesterone, or DHEA-S<br>• No difference in 6 urinary steroids (primarily androgens)<br>• Overall effect was not significant | Adjusted serum values for cycle day, age, and BMI; adjusted urine values for age, BMI, and parity |
| Berta et al. 1992 | • 684 nonobese fertile women<br>• 25–52 years of age | 24-hour urine sample and 3 blood samples on days 21–24 of LP | Smoker (n = 237): >10 cig/ per day for ≥5 years | • Plasma progesterone decreased 15% (p <0.05)<br>• Plasma prolactin decreased 20% (p <0.002)<br>• No difference in E1 and E2 | Age did not affect results |
| Daniel et al. 1992 | • 52 women<br>• 20–35 years of age | Blood collected after overnight fast | Current smoker (n = 25): 16.9 (mean) cigarettes/day<br>Former smoker (n = 11) | • No difference in cortisol, E2, and testosterone<br>• Levels of cortisol, E2, and testosterone were not significant in adjusted model<br>• SHBG increased (p <0.006) | Age, height, and weight were similar in both groups; data were adjusted for sum of 8 skinfold thicknesses |

**Table 6.11*S* Continued**

| Study | Population | Sample/period | Definition of smoking (number of subjects) | Findings among smokers: Estimate of effect (95% CI or p value) | Comments |
|---|---|---|---|---|---|
| Thomas et al. 1993 | • 46 fertile, premenopausal women | Blood, saliva, and urine samples collected on days 8, 9–11, 12, 13–17, and 18 of menses | Smoker (n = 25): >5 cigarettes/day for ≥1 year | • No difference in plasma E2 during FP<br>• No difference in salivary progesterone during LP<br>• No difference in plasma testosterone, androstenedione, SHBG, and DHEA-S<br>• No difference in urinary E1, E2, and E3<br>• Overall effect was not *s*ignificant | Data suggest that antiestrogenic effect does not work through changes in estrogen metabolism or pituitary/follicular endocrine function |
| Cramer et al. 1994 | • 224 women, some with a family history of ovarian cancer<br>• 26–50 years of age | 1 blood sample during early FP (days 1–3) | Current smoker (n = 42) | • Mean FSH increased 14–21% (p = 0.03) in current and former smokers (>10 pack-years) | Effect of smoking was still significant after adjusting for age |
| Cooper et al. 1995 | • 290 women<br>• 38–49 years of age | 1 blood sample during early FP (days 2–4) | Current smoker (n = 31): smoked in past 2 years | • Mean FSH increased 66% (28–116%) in current smokers<br>• Mean FSH increased 57% at <10 cigarettes/day<br>• Mean FSH increased 76% at 10–20 cigarettes/day<br>• Mean FSH increased 39% (4–86) in those exposed to SHS<br>• No difference in FSH in former smokers or prenatal exposure | None of the factors examined were confounders; significant interaction with age; effects investigated during menopausal transition period |
| Key et al. 1996 | • Women recruited from Guernsey Breast Cancer Study (n = 167)<br>• ≥34 years of age | 24-hour urine sample collected 3–11 days after onset of menstruation (FP) or 3–11 days before (LP) | Current smoker (n = 53) | • E1 decreased 0–16%<br>• E2 decreased 4–15%<br>• E3 decreased 30% during early FP<br>• E3 decreased 5–22% later in cycle | Findings were not significant after adjusting for time of cycle, age, and BMI |
| Westhoff et al. 1996 | • 175 parous women with normal length menstrual cycles<br>• 21–36 years of age | Daily first-morning urine sample on day 10 of menses<br>Blood sample three times during LP | Current smoker (n = 48) | • No difference in mean LP progesterone in blood or urine<br>• E2 in urine decreased 21% (p = 0.04) during LP | Four anovulatory women were excluded; adjusted for creatine (decreased differences in E2); some dose-response effects |

**Table 6.11*S* Continued**

| Study | Population | Sample/period | Definition of smoking (number of subjects) | Findings among smokers: Estimate of effect (95% CI or p value) | Comments |
|---|---|---|---|---|---|
| Backer et al. 1999 | • 3,114 women from the National Health and Nutrition Examination Survey (United States national sample)<br>• 36–60 years of age | 1 convenient blood sample | Smoker: smoked during 5 days before examination | • Increased FSH ($p < 0.001$) | Cycle timing was unknown, but tried to exclude samples obtained close to time of ovulation on basis of LH-to-FSH ratio |
| Lucero et al. 2001 | • 498 women, not in a depressive state, from Harvard Study of Moods and Cycles<br>• 36–44 years of age | 1 blood sample during early FP (days 1–5) | Current smoker (n = 52)<br>Former smoker (n = 72) | • FSH increased 12% ($p < 0.05$)<br>• E2 increased 8% ($p < 0.05$)<br>• No difference in LH or SHBG | E2 was not significant in adjusted model; FSH values were not adjusted; findings for current smokers adjusted for age, BMI, calories, use of alcohol and caffeine, cholesterol, and cycle day; no difference between current smokers and former smokers, no dose-response effect |
| Sowers et al. 2001 | • 611 women from the Michigan Bone Health & Metabolism Study<br>• 25–50 years of age | Blood sample drawn once per year after an 8-hour fast on days 3–7 of FP | Current, former, and never smoker | • Increased testosterone levels in current and former smokers ($p < 0.0001$) | Adjusted for factors, including BMI |
| Verkasalo et al. 2001 | • 636 women who reported having ≥10 menstrual cycles during previous 12 months<br>• 20–44 years of age | Blood sample | Current smoker (n = 49)<br>Former smoker (n = 171)<br>Never smoker (n = 416) | • Increased E2 in smokers compared with former and never smokers ($p = 0.003$)<br>• No difference in SHBG, FSH, progesterone, and LH | Adjusted for age, BMI, physical activity, use of alcohol, family history of breast cancer, age at menarche, etc. |
| Jernström et al. 2003 | • 513 nulliparous women<br>• 17–35 years of age | Morning blood sample on random day (timing calculated) | Current smoker (yes/no) | • 2OHE/16α-OHE increased slightly (19%) before adjustment ($p = 0.06$) but not after adjustment ($p = 0.76$) among women not using oral contraceptives<br>• No effect on either metabolite alone | Adjusted for age, race, and cycle day |

**Table 6.11*S* Continued**

| Study | Population | Sample/period | Definition of smoking (number of subjects) | Findings among smokers: Estimate of effect (95% CI or p value) | Comments |
|---|---|---|---|---|---|
| Windham et al. 2005 | • 403 women in reproductive years from the Kaiser Permanente health maintenance organization | Daily urine sample collected through 2–7 cycles<br>Adjustment of hormone values for creatinine | Smoker: cigarettes/day, from daily diary and averaged over 100–150 cycles | • Mean FSH increased 20–35% and was significant on some days<br>• Mean FSH increased at >10 cigarettes/day<br>• During early FP, E1 conjugates (estrone sulfate and estrone glucuronide) increased 25% and progesterone metabolites increased 35% ($p < 0.05$) at >10 cigarettes/day<br>• During LP, progesterone decreased 25% ($p = 0.06$) at >20 cigarettes/day | Adjusted for age, race, history of pregnancy, BMI, and use of alcohol and caffeine; some dose-response effects |
| Gallicchio et al. 2006 | • 353 pre- and perimenopausal women<br>• 45–54 years of age | Blood sample collected in morning | Current smoker (n = 25)<br>Former smoker (n = 235) | • No difference in E2 and E1<br>• Overall effect was not significant | Findings were based on univariate analyses only |
| Cochran et al. 2008 | • 628 pre- and perimenopausal women<br>• 45–54 years of age | Blood sample collected in morning | Current smoker (n = 58)<br>Former smoker (n = 242) | • Current smokers had increased levels of androstenedione ($p = 0.01$) and increased androgen/estrogen ratios ($p = 0.04$)<br>• Former and current smokers had decreased levels of progesterone ($p = 0.04$) | Adjusted for age, race, BMI, current use of alcohol, and number of days since last menstrual period |

*Note:* **2OHE** = 2-hydroxyestrone; **16α-OHE** = 16α-hydroxyestrone; **BMI** = body mass index; **CI** = confidence interval; **DHEAS** = dehydroepiandrosterone sulfate; **E1** = estrone; **E2** = estradiol; **E3** = estriol; **FP** = follicular phase; **FSH** = follicle-stimulating hormone; **LH** = lutenizing hormone; **LP** = luteal phase; **OHE** = hydroxyestrone; **pack-years** = the number of years of smoking multiplied by the number of packs of cigarettes smoked per day; **SHBG** = sex hormone binding globulin; **SHS** = secondhand smoke.

**Table 6.12*S*  Reports on levels of endogenous hormones and smoking in postmenopausal women (n = 17)**

| Study | Study population | Sample/period | Definition of smoking (number of subjects) | Findings in smokers: Estimate of effect (95% CI or p value) | Comments |
|---|---|---|---|---|---|
| Ernster et al. 1987 | • 289 women | Breast fluid by nipple aspiration and blood sample | Current, former, and never smoker | • No difference in E1, E2, and SHBG in breast fluid or serum<br>• Overall effect was not significant | Adjusted for menopausal estrogen use and thyroid hormone use |
| Friedman et al. 1987 | • 25 women, after natural menopause and between 1.5–6 years before the study | Morning blood sample after 12-hour fast | Smoker (n = 9) for >20 years | • Smokers had increased levels of cortisol ($p < 0.001$), progesterone ($p < 0.05$), 17-hydroxyprogesterone ($p < 0.0005$), androstenedione ($p < 0.05$), and testosterone ($p < 0.05$)<br>• No difference in E1, E2, dihydrotestosterone, and dehyroepiandrosterone sulfate | No difference in BMI or age at menopause |
| Trichopoulous et al. 1987 | • 220 women, ≥1 year after menopause<br>• 54–66 years of age | Overnight urine sample | Current smoker (n = 97) | • Smokers had increased levels of DHEAS ($p < 0.001$) and androstenedione ($p = 0.003$)<br>• No difference in E1, E2, testosterone, and SHBG | Dose-response trend was observed; adjusted for age and BMI |
| Khaw et al. 1988 | • 233 White women<br>• 60–79 years of age | Plasma sample | Current smoker (n = 46) | • Decreased metabolic clearance rates for testosterone, androstenedione, and E1 were not significant in premenopausal women ($p < 0.05$)<br>• Increased plasma androstenedione ($p < 0.02$)<br>• No difference in E1 and E2<br>• No difference in SHBG, steroid production rates, and aromatization of androgens | No difference after adjusting for weight; no interaction between menopausal status and smoking for any of the variables |
| Longcope and Johnston 1988 | • 88 women (47 premenopausal)<br>• Age (mean): 50 years | Radiolabeled steroid infusion<br>Blood and urine samples at baseline | Smoker (n = 23): 10 cigarettes/day for ≥10 years | • Metabolic clearance rates decreased for testosterone, androstenedione, and E1 were not significant in premenopausal women ($p < 0.05$)<br>• Increased plasma androstenedione ($p < 0.02$)<br>• No difference in E1 and E2<br>• No difference in SHBG, steroid production rates, and aromatization of androgens | No difference after adjusting for weight; no interaction between menopausal status and smoking for any of variables |

**Table 6.12*S* Continued**

| Study | Study population | Sample/period | Definition of smoking (number of subjects) | Findings in smokers: Estimate of effect (95% CI or p value) | Comments |
|---|---|---|---|---|---|
| Cauley et al. 1989 | • 176 White women | Fasting blood sample | Current smoker (n = 26) | • Smokers had increased levels of androstenedione (p <0.01)<br>• No difference in E1, E2, and testosterone | Adjusted for BMI, use of alcohol (ounces/day), age, and physical activity |
| Slemenda et al. 1989 | • 84 peri- and postmenopausal women | Blood drawn every 4 months | <20 pack-years (n = 8)<br>>20 pack-years (n = 13) | • No difference in serum E1, E2, testosterone, or androstenedione<br>• Overall effect was not significant | Hormone levels based on the average of approximately 12 measurements/subject |
| Schlemmer et al. 1990 | • 267 women, after natural menopause and between 6 months and 1 year before the study<br>• 45–54 years of age | Blood sample after overnight fast and tobacco abstinence | Smoker (n = 146): ≥3 cigarettes/day during 6 months before the study | • Smokers had a 22% increase in androstenedione (p <0.001) and increased levels of LH (p = 0.06)<br>• No difference in E1, E2, and FSH | No dose-response effect was observed; body weight and age at menopause differed by smoking status |
| Key et al. 1991 | • Women recruited from the Guernsey Breast Cancer Study with menstrual cycle lengths of 21–35 days<br>• ≥35 years of age | 24-hour urine sample and 1 blood sample | Current smoker: 1–10, 11–20, and ≥21 cigarettes/day<br>E2 and progesterone (n = 69)<br>DHEA-S (n = 97)<br>Urinary steroids (n = 20) | • No difference in serum E2, progesterone, or DHEA-S<br>• No difference in 6 urinary steroids (primarily androgens)<br>• Overall effect was not significant | Adjusted serum values for cycle day, age, and BMI; adjusted urine values for age, BMI, and parity |
| Cassidenti et al. 1992 | • 38 postmenopausal women | Blood collected in morning before first cigarette and 3 hours later (after 5 cigarettes) | Current smoker (n = 21) | • After 5 cigarettes, smokers had a 52% increase of baseline androstenedione (p = 0.011)<br>• No significant increase of DHEA-S and cortisol in smokers<br>• No difference in E1, E2, or E3 | Adjusted for age, age at menopause, weight, height, and use of alcohol |
| Baron et al. 1995 | • 22 women<br>• ≥55 years of age | Blood samples every hour for 8 hours before/after cigarette/sham and before/after corticotrophin stimulation test | Smoker (n = 11): 0.5–1.5 packs of filtered cigarettes/day | • Smokers had increased basal levels of androstenedione (p <0.05) and DHEAS (p <0.05)<br>• Smokers had elevated average levels of cortisol (p = 0.03) and androstenedione (p <0.05)<br>• No difference in response to corticotropin stimulation | No difference after adjusting for age, BMI, and use of alcohol |

**Table 6.12*S* Continued**

| Study | Study population | Sample/period | Definition of smoking (number of subjects) | Findings in smokers: Estimate of effect (95% CI or p value) | Comments |
|---|---|---|---|---|---|
| Newcomb et al. 1995 | • 253 women from the Beaver Dam Eye Study | Serum sample | 20% current smokers | • No difference in E1, DHEA-S, SHBG, and testosterone<br>• Overall effect was not significant | Adjusted for age, BMI, and years since menopause |
| Key et al. 1996 | • 200 women recruited from the Guernsey Breast Cancer Study | 24-hour urine sample | Current smoker (n = 54) | • No difference in E1 and E2<br>• Smokers had a 19% decrease in levels of E3 (34–1) | Not significant after adjusting for age and BMI |
| Law et al. 1997 | • 194 White postmenopausal women<br>• 35–64 years of age | Serum sample | Current smoker (n = 40)<br>Former smoker (n = 44) | • No difference in E1, E2, cortisol, FSH, LH, SHBG, androstenedione, and prolactin<br>• Overall effect was not significant | No difference observed in former smokers; no difference after adjusting for such factors as exercise, OC, corticosteroids, age at menarche and menopause, etc. |
| Verkasalo et al. 2001 | • 456 postmenopausal women with no menstrual cycle during previous 12 months<br>• ≥55 years of age | Blood sample | Current smoker (n = 15)<br>Former smoker (n = 42)<br>Never smoker (n = 299) | • No difference in E2 and SHBG<br>• Overall effect was not significant | Adjusted for BMI, use of alcohol, age at menarche, physical activity, etc. |
| Manjer et al. 2005 | • 336 women from the Malmo Diet and Cancer Study and The Northern Sweden Health and Disease Study | Blood sample | Current smoker (n = 91)<br>Former smoker (n = 82) | • Current smokers had high levels of testosterone: AOR = 1.85 (1.06–3.23)<br>• No difference in levels of androstenedione and DHEAS | Adjusted for age, education level, age at menarche and at menopause, OC, use of hormone replacement therapy, etc.; no dose-response effect observed |
| Danforth et al. 2010 | • 646 postmenopausal women from the Nurses' Health Study | Blood sample | Current smoker (n = 83)<br>Former smoker (n = 260) | • Those who smoked >25 cigarettes/day had a 35% increase in androstenedione (p = 0.03), a 44% increase in testosterone (p = 0.01), and elevated levels of DHEA-S (p = 0.05)<br>• No difference in DHEA and testosterone | No dose-response observed; adjusted for such factors as BMI, use of alcohol, family history of breast or ovarian cancer, etc. |

*Note:* **AOR** = adjusted odds ratio; **BMI** = body mass index; **CI** = confidence interval; **DHEA-S** = dehydroepiandrosterone sulfate; **E1** = estrone; **E2** = estradiol; **E3** = estriol; **FSH** = follicle-stimulating hormone; **LH** = lutenizing hormone; **OC** = oral contraceptive; **pack-years** = the number of years of smoking multiplied by the number of packs of cigarettes smoked per day; **SHBG** = sex hormone binding globulin.

**Table 6.14*S* Cohort study reports of the association between active cigarette smoking and risk of breast cancer, based on studies published before 2012 (n = 15)**

| Study | Design/population | Number of breast cancer events | Data collection/subgroup analyses | Findings for active cigarette smoking | Measures of active cigarette smoking: RR (95% CI) | Confounders |
|---|---|---|---|---|---|---|
| Manjer et al. 2000b[a] | • Malmö Department of Preventative Medicine<br>• 10,902 women enrolled from 1974–1992 to evaluate risk factors associated with CVD<br>• Average follow-up: 13.6 years<br>• Age (mean): 49.7 years<br>• Sweden | 416 incident cases (in situ, invasive) | • Self-administered questionnaire at enrollment<br>• Data collected for smoking status (never, former, current), amount of daily consumption (current), and time since cessation (former)<br>• Subgroups stratified by menopausal status | • Significantly increased risk for breast cancer among former smokers, primarily due to association in premenopausal women | **Status:**<br>Never: 1.00<br>Former: 1.31 (1.02–1.69)<br>Current: 1.08 (0.86–1.35)<br>**Status: Premenopausal**<br>Never: 1.00<br>Former: 1.57 (1.07–2.30)<br>Current: 1.19 (0.85–1.68)<br>**Status: Postmenopausal**<br>Never: 1.00<br>Former: 1.15 (0.82–1.62)<br>Current: 1.00 (0.74–1.35) | Controlled for age at baseline, height, BMI, parity, OC use, HRT, alcohol use, and menstrual status |
| Manjer et al. 2001[a] | • Malmö Department of Preventative Medicine<br>• 10,902 women enrolled from 1974–1992 to evaluate risk factors associated with CVD<br>• Average follow-up: 12.4 years<br>• Age (mean): 49.7 years Sweden | 268 incident cases (invasive) | • Self-administered questionnaire at enrollment<br>• Data collected for smoking status (never, former, current), amount of daily consumption (current), and time since cessation (former)<br>• Subgroups evaluated and stratified by ER/PR status and histopathology type | • Trend towards increased risk with cigarettes/day<br>• Increased risk of ER– tumors for current and former smokers<br>• No association with histopathology type or tumor differentiation | **Status:**<br>Never: 1.00<br>Former: 1.34 (0.99–1.81)<br>Current: 1.10 (0.84–1.44)<br>≤19 cig/day: 1.05 (0.78–1.42)<br>≥20 cig/day: 1.17 (0.78–1.76) | Controlled for age at baseline, height, BMI, age at menarche, menopause status, parity, OC use, HRT, education, marital status, and alcohol use |

**Table 6.14*S* Continued**

| Study | Design/population | Number of breast cancer events | Data collection/subgroup analyses | Findings for active cigarette smoking | Measures of active cigarette smoking: RR (95% CI) | Confounders |
|---|---|---|---|---|---|---|
| Egan et al. 2002[a] | • Nurses' Health Study-I<br>• 121,700 nurses enrolled in 1976 to evaluate risk factors for breast cancer and CVD<br>• 78,206 women included in the analysis<br>• Average follow-up: 14 years<br>• 30–55 years of age<br>• United States | 3,140 incident cases (invasive) | • Self-administered questionnaire at enrollment; biennial questionnaires until 1994<br>• Data collected for smoking status (never, former, and current), cigarettes/day, duration and timing related to birth of first child<br>• Data collected for secondhand smoke exposure (see USDHHS 2006) | • Increased risk of breast cancer in former smokers<br>• Further increased risk when based on a no active/no passive referent group<br>• Significant trend observed for years of smoking before first birth | **Status:**<br>Never: 1.00<br>Former: 1.09 (1.00–1.18)<br>Current: 1.04 (0.94–1.15)<br>**Status With NA/NP:**<br>NA/NP: 1.00<br>Former: 1.17 (1.01–1.34)<br>Current: 1.15 (0.98–1.34)<br>**Duration (Years):**<br>Never: 1.00<br><20: 1.04 (0.95–1.15)<br>20–29: 1.11 (1.00–1.24)<br>30–39: 1.08 (0.97–1.21)<br>>40: 1.05 (0.90–1.21)<br>p trend = 0.18<br>**Age at Smoking Initiation:**<br>Never: 1.00<br>>22: 1.06 (0.92–1.22)<br>21–22: 1.04 (1.91–1.18)<br>19–20: 1.11 (1.00–1.13)<br>17–18: 1.02 (0.92–1.13)<br><17: 1.19 (1.03–1.37)<br>p trend = 0.13<br>**Age at Smoking Initiation:**<br>Never: 1.00<br>>16: 1.12 (0.96–1.31)<br>≤16: 1.31 (1.07–1.31)<br>**Timing With First Pregnancy: Before (Years)**<br>Never: 1.00<br><5: 1.10 (0.96–1.26)<br>≥5: 1.13 (0.99–1.30)<br>p trend = 0.03<br>**After (Years)**<br>Never: 1.00<br><10: 0.95 (0.81–1.12)<br>10–20: 0.98 (0.83–1.14)<br>>20: 0.99 (0.86–1.13)<br>p trend = 0.90 | Controlled for age, age at menarche, age at birth of first child, history of benign disease, family history of breast cancer, menopausal status, age at menopause, weight, height, alcohol use, dietary factors, HRT |

**Table 6.14*S* Continued**

| Study | Design/population | Number of breast cancer events | Data collection/subgroup analyses | Findings for active cigarette smoking | Measures of active cigarette smoking: RR (95% CI) | Confounders |
|---|---|---|---|---|---|---|
| Terry et al. 2002a[a] | • Canadian National Breast Screening Study<br>• 89,835 women enrolled from 1980–1985 into a multicenter, randomized controlled trial of mammographic screening<br>• Average follow-up: 10.6 years<br>• 40–59 years of age<br>• Canada | 2,552 incident cases (in situ, invasive) | • Self-administered questionnaire at enrollment<br>• Data collected for smoking status (never, former, current), cigarettes/day, duration, and years since smoking cessation | • Risk of breast cancer was associated with current but not former smoking<br>• Risk was significantly associated with cigarettes/day, duration, and pack-years of smoking<br>• No association between age at smoking initiation and number of years since smoking cessation | **Status:**<br>Never: 1.00<br>Former: 0.99 (0.90–1.09)<br>Current: 1.14 (1.03–1.27)<br>**Duration (Years):**<br>Never: 1.00<br>1–9: 0.93 (0.80–1.09)<br>10–19: 0.97 (0.85–1.11)<br>20–29: 1.06 (0.94–1.19)<br>30–39: 1.14 (0.99–1.31)<br>≥40: 1.61 (1.19–2.19)<br>p trend = 0.009<br>**Cigarettes/Day:**<br>Never: 1.00<br>1–9: 0.97 (0.85–1.11)<br>10–19: 0.98 (0.86–1.11)<br>20–29: 1.10 (0.99–1.23)<br>30–39: 0.90 (0.71–1.16)<br>≥40: 1.34 (1.06–1.69)<br>p trend = 0.05<br>**Pack-years:**<br>Never: 1.00<br>1–9: 0.98 (0.87–1.10)<br>10–19: 0.97 (0.85–1.12)<br>20–29: 1.08 (0.93–1.25)<br>30–39: 1.21 (1.04–1.42)<br>≥40: 1.37 (1.15–1.62)<br>p trend = 0.003<br>**Age at Smoking Initiation:**<br>Never: 1.00<br>≥20: 1.04 (0.95–1.14)<br>16–19: 1.05 (0.96–1.18)<br><16: 1.10 (0.86–1.42)<br>p trend = 0.23 | Controlled for age, treatment, study center, BMI, education, physical activity, OC use, HRT, parity, age at menarche, history of benign breast disease, breast self-exam, family history, menopausal status, alcohol use |

**Table 6.14*S* Continued**

| Study | Design/population | Number of breast cancer events | Data collection/subgroup analyses | Findings for active cigarette smoking | Measures of active cigarette smoking: RR (95% CI) | Confounders |
|---|---|---|---|---|---|---|
| Al-Delaimy et al. 2004 | • Nurses' Health Study-II<br>• 116,671 nurses enrolled in 1989 to evaluate risk factors for CVD and breast cancer<br>• Average follow-up: 10 years<br>• 25–42 years of age<br>• United States | 1,009 incident cases (invasive) | • Self-administered questionnaire at enrollment and biennial thereafter<br>• Data collected for smoking status (never, former, current), cigarettes/day, duration, smoking before first pregnancy, and smoking before or after 20 years of age<br>• Subgroups evaluated and stratified by ER status; vitamin A and carotenoid intake | • No overall association with smoking status or pack-years<br>• Risk was significantly associated with duration of smoking and years of smoking before first pregnancy<br>• Age at initiation and pack-years of smoking were associated more strongly with ER+ than ER– tumor phenotype (results not shown) | **Status:**<br>Never: 1.00<br>Former: 1.18 (1.02–1.36)<br>Current: 1.12 (0.92–1.37)<br>**Duration (Years):**<br>Never: 1.00<br><10: 1.14 (0.85–1.52)<br>10–14: 1.19 (0.96–1.48)<br>15–19: 1.06 (0.85–1.33)<br>≥20: 1.21 (1.01–1.45)<br>p trend = 0.04<br>**Cigarettes/Day:**<br>Never: 1.00<br>1–4: 0.77 (0.44–1.33)<br>5–14: 1.18 (0.88–1.74)<br>15–24: 1.14 (0.90–1.61)<br>≥25: 0.98 (0.69–1.70)<br>p trend = 0.40<br>**Cigarettes/Day: Former Smokers**<br>Never: 1.00<br>1–4: 1.21 (0.94–1.56)<br>5–14: 1.32 (1.06–1.65)<br>15–24: 1.04 (0.82–1.33)<br>≥25: 1.12 (0.82–1.53)<br>p trend = 0.60<br>**Pack-years:**<br>Never: 1.00<br><10: 1.16 (0.98–1.39)<br>10–24: 1.16 (0.97–1.38)<br>≥25: 1.13 (0.86–1.50)<br>p trend = 0.20<br>**Age at Smoking Initiation:**<br>Never: 1.00<br>≥20: 1.18 (0.97–1.42)<br>15–19: 1.09 (0.93–1.29)<br><15: 1.29 (0.97–1.71)<br>**Timing With First Pregnancy: Before (Years)**<br>Never: 1.00<br>1–4: 1.02 (0.72–1.44)<br>5–9: 1.12 (0.91–1.39)<br>10–14: 1.19 (0.97–1.47)<br>15–19: 1.42 (1.10–1.83)<br>≥20: 1.10 (0.80–1.52)<br>p trend = 0.01 | Controlled for age, BMI, height, oral contraceptive use, parity, age at birth of first child, age at menarche, family history, benign breast disease, alcohol use, and menopausal status |

**Table 6.14*S* Continued**

| Study | Design/population | Number of breast cancer events | Data collection/subgroup analyses | Findings for active cigarette smoking | Measures of active cigarette smoking: RR (95% CI) | Confounders |
|---|---|---|---|---|---|---|
| Lawlor et al. 2004 | • British Women's Heart and Health Study<br>• 4,286 women (85% post-menopausal) enrolled from 1999–2001 to evaluate risk factors for breast cancer<br>• Analysis restricted to 3,047 women with at least 1 live birth<br>• Average follow-up: 3.5 years<br>• 60–79 years of age<br>• United Kingdom | 139 incident and prevalent cases (invasive) | • Self-administered questionnaire, physical exam, and review of medical records at enrollment with update at 3-year follow-up<br>• Data collected for smoking status (never, former, and current), age at initiation, and smoking in relation to first pregnancy<br>• Subgroups evaluated by menopause (data not provided) | • No significant association was found with any smoking measure<br>• No difference in risk when analysis restricted to postmenopausal women (results not shown) | **Timing With First Pregnancy: Incident Cases**<br>Never: 1.00<br>Before: 1.08 (0.39–2.55)<br>**Timing With First Pregnancy: Incident and Prevalent Cases**<br>Never: 1.00<br>Before: 1.04 (0.68–1.57)<br>After: 0.70 (0.36–1.36)<br>**Within 5 Years of Menarche: Incident and Prevalent Cases**<br>Never: 1.00<br>±5 years: 1.00 (0.70–1.39) | Controlled for age, parity, age at menarche, age at menopause, hysterectomy, HRT, OC use, social class during childhood and adulthood, and BMI |

**Table 6.14*S* Continued**

| Study | Design/population | Number of breast cancer events | Data collection/subgroup analyses | Findings for active cigarette smoking | Measures of active cigarette smoking: RR (95% CI) | Confounders |
|---|---|---|---|---|---|---|
| Reynolds et al. 2004b | • California Teachers Study<br>• 329,000 women enrolled from 1995–2000 to evaluate risk factors for breast cancer<br>• 116, 544 women included in the analysis<br>• Average follow-up: 5 years<br>• >20 years of age<br>• California | 2,005 incident cases (in situ, invasive) | • Self-administered questionnaire at enrollment<br>• Data collected for smoking status (never, former, and current), cigarettes/day, duration, pack-years, age at initiation, and in relation to first pregnancy<br>• Data collected for secondhand smoke exposure (see USDHHS 2006)<br>• Analyses based on the full sample includes a category for women with unknown menopausal status<br>• Subgroups evaluated and stratified by menopausal status and family history of breast cancer | • Significant increased risk for current smokers (including both no active and NA/NP referent groups)<br>• Risk mainly increased in postmenopausal current smokers<br>• Increased risk in women who smoked ≥5 years before first pregnancy, with no difference by menopausal status<br>• Significant trend for increased risk with duration of smoking, especially in postmenopausal women<br>• Significant trend for increased risk with cigarettes/day and pack-years of smoking<br>• Significant increased risk for women who started smoking before 20 years of age | **Status:**<br>Never: 1.00<br>Former: 1.08 (0.98–1.19)<br>PreM: 1.12 (0.89–1.42)<br>PostM: 1.07 (0.95–1.20)<br>Current: 1.32 (1.10–1.57)<br>PreM: 1.02 (0.60–1.72)<br>PostM: 1.29 (1.05–1.58)<br>**Status With NA/NP:**<br>NA/NP: 1.00<br>NA/Passive: 0.94 (0.82–1.07)<br>PreM: 0.93 (0.71–1.22)<br>PostM: 0.92 (0.78–1.08)<br>Former: 1.03 (0.89–1.18)<br>PreM: 1.07 (0.79–1.44)<br>PostM: 1.01 (0.85–1.19)<br>Current: 1.25 (1.02–1.53)<br>PreM: 0.96 (0.55–1.68)<br>PostM: 1.21 (0.95–1.54)<br>**Duration (Years):**<br>Never: 1.00<br><10: 0.99 (0.85–1.17)<br>11–20: 1.17 (1.00–1.37)<br>21–30: 1.17 (0.99–1.38)<br>≥31: 1.15 (1.00–1.33)<br>p trend = 0.009<br>**Duration (Years): Premenopausal**<br>Never: 1.00<br><10: 1.14 (0.85–1.55)<br>11–20: 1.10 (0.76–1.58)<br>21–30: 1.06 (0.67–1.66)<br>≥31: 0.99 (0.46–2.13)<br>p trend = 0.616 | Controlled for age, race, family history, age at menarche, pregnancy history, physical activity, BMI, menopausal status, interaction between BMI and menopausal status, alcohol use, and HRT |

**Table 6.14*S* Continued**

| Study | Design/population | Number of breast cancer events | Data collection/subgroup analyses | Findings for active cigarette smoking | Measures of active cigarette smoking: RR (95% CI) | Confounders |
|---|---|---|---|---|---|---|
| Reynolds et al. 2004b (continued) | | | | | **Duration (Years):**<br>**Postmenopausal**<br>Never: 1.00<br><10: 0.95 (0.77–1.17)<br>11–20: 1.22 (1.02–1.47)<br>21–30: 1.07 (0.88–1.31)<br>≥31: 1.16 (0.99–1.34)<br>p trend = 0.032<br>**Cigarettes/Day:**<br>Never: 1.00<br><10: 1.04 (0.92–1.18)<br>10–19: 1.14 (0.99–1.30)<br>≥20: 1.22 (1.05–1.42)<br>p trend = 0.004<br>**Pack-years:**<br>Never: 1.00<br><10: 1.02 (0.91–1.16)<br>11–20: 1.24 (1.05–1.46)<br>21–30: 1.12 (0.91–1.39)<br>≥31: 1.25 (1.06–1.47)<br>p trend = 0.002<br>**Age at Smoking Initiation:**<br>Never: 1.00<br>≥20: 1.03 (0.90–1.17)<br><20: 1.17 (1.05–1.30)<br>**Timing With First Pregnancy:**<br>Never: 1.00<br>Before<br><5 years: 0.99 (0.80–1.21)<br>≥5 years: 1.13 (1.00–1.28)<br>After: 0.89 (0.65–1.21) | |

**Table 6.14*S* Continued**

| Study | Design/population | Number of breast cancer events | Data collection/subgroup analyses | Findings for active cigarette smoking | Measures of active cigarette smoking: RR (95% CI) | Confounders |
|---|---|---|---|---|---|---|
| Gram et al. 2005 | • Norwegian-Swedish Cohort Women's Lifestyle and Health Study<br>• 102,098 women were enrolled in 1991–1992 to evaluate risk factors for multiple health outcomes<br>• Average follow-up: 8-9 years<br>• 30–50 years of age<br>• Norway and Sweden | 1,240 incident breast cancer cases (invasive) | • Self-administered questionnaire at enrollment<br>• Data collected for smoking status (never, former, current), duration, cigarettes/day, pack-years, smoking before first pregnancy and before and after menarche<br>• Data collected for secondhand smoke exposure (see Table 6.22*S*)<br>• Subgroups evaluated by alcohol use | • Estimates based on both no active and NA/NP referent groups<br>• Significant trends for smoking duration, pack-years and cigarettes/day among current smokers compared to a NA/NP referent group (n = 28,624)<br>• Similar and slightly higher risks for ever smokers with 20+ years of smoking (n = 26,724)<br>• Analyses restricted to nondrinkers generally showed higher risk estimates for both long-term and current smokers | **Status:**<br>Never: 1.00<br>Ever: 1.00 (0.98–1.50)<br>**Status With NA/NP:**<br>NA/NP: 1.00<br>Passive: 1.21 (0.98–1.50)<br>Former: 1.15 (0.94–1.41)<br>Current: 1.17 (0.95–1.40)<br>**Duration (Years) With NA/NP:**<br>NA/NP: 1.00<br>1–19: 0.93 (0.68–1.28)<br>20–24: 1.09 (0.81–1.45)<br>≥25: 1.26 (0.98–1.63)<br>p trend = 0.05<br>**Cigarettes/Day With NA/NP:**<br>NA/NP: 1.00<br>1–9: 0.96 (0.74–1.25)<br>≥10: 1.28 (1.01–1.63)<br>p trend = 0.03<br>**Pack-years With NA/NP:**<br>NA/NP: 1.00<br>0–14: 0.95 (0.74–1.20)<br>15–19: 1.28 (0.96–1.72)<br>≥20: 1.48 (1.14–1.96)<br>p trend = 0.001<br>**Age at Smoking Initiation With NA/NP:**<br>NA/NP: 1.00<br>≥20: 1.02 (0.78–1.35)<br>15–19: 1.15 (0.91–1.47)<br>10–14: 1.51 (1.00–2.28)<br>p trend = 0.07<br>**Timing With First Pregnancy With NA/NP: Before**<br>NA/NP: 1.00<br>No: 0.99 (0.72–1.37)<br>Yes: 1.18 (0.92–1.52)<br>p trend = 0.14 | Controlled for age, menopausal status, number of children, age at birth of first child, HRT, BMI, and alcohol use |

**Table 6.14*S* Continued**

| Study | Design/population | Number of breast cancer events | Data collection/subgroup analyses | Findings for active cigarette smoking | Measures of active cigarette smoking: RR (95% CI) | Confounders |
|---|---|---|---|---|---|---|
| Hanaoka et al. 2005 | • Japan Public Health Center<br>• 27,398 women enrolled in 1990 to evaluate risk factors for cancer and CVD<br>• 21,805 women included in the analysis<br>• Average follow-up: 10 years<br>• 40–59 years of age<br>• Japan | 180 incident cases (invasive) | • Self-administered questionnaire at enrollment<br>• Data collected for smoking status (never, former, and current), age at initiation and cessation, and smoking intensity and duration<br>• Data for cancer incidence and mortality collected through 1999 by a cancer registry established for the Japan Public Health Center and a registry of deaths in Japan<br>• Data collected for exposure to secondhand smoke (see USDHHS 2006)<br>• Subgroups evaluated and stratified by menopausal status | • Significantly increased risk for breast cancer among current smokers<br>• When excluding women with exposure to secondhand smoke from the referent group, the RR increased 10-20% compared with results based on a no-active only referent group<br>• Risk primarily observed among premenopausal women | **Ever With NA/NP: Premenopausal**<br>NA/NP: 1.00<br>Passive: 2.60 (1.30–5.20)<br>Ever, active: 3.90 (1.50–9.90)<br>**Ever With NA/NP: Postmenopausal**<br>NA/NP: 1.00<br>Passive: 0.60 (0.40–1.00)<br>Ever, active: 1.10 (0.50–2.50)<br>**Status:**<br>Never: 1.00<br>Former: 1.10 (0.40–3.50)<br>Current: 1.70 (1.00–3.10)<br>**Status With NA/NP:**<br>NA/NP: 1.00<br>Passive: 1.10 (0.80–1.60)<br>Former: 1.20 (0.40–4.00)<br>Current: 1.90 (1.00–3.60) | Controlled for age, geographic area, education, employment status, BMI, family history of breast cancer, benign breast disease, age at menarche, parity, menopausal status, HRT, and alcohol use |
| Olson et al. 2005 | • Iowa Women's Health Study<br>• 41,386 enrolled in 1986<br>• 37,105 women included in the analysis<br>• Average follow-up: 14 years<br>• 55–69 years of age<br>• United States | 2,017 incident cases (stage not specified) | • Self-administered questionnaire at enrollment and at follow-up (1987, 1989, 1992, and 1997)<br>• Data for active cigarette smoking collected for smoking status (never, former, current) and timing in relation to first pregnancy<br>• Subgroups evaluated and stratified by childbearing history and parity | • Significantly increased risk in current smokers<br>• Risk significantly increased with long duration of smoking (>40 years)<br>• Risk significantly increased among women who initiated smoking after 18 years of age<br>• Risk significantly increased with smoking before first pregnancy | **Status:**<br>Never: 1.00<br>Former: 1.08 (0.95–1.22)<br>Current: 1.19 (1.03–1.37)<br>**Duration (Years):**<br>Never: 1.00<br>1–19: 1.01 (0.83–1.21)<br>20–39: 1.13 (0.99–1.29)<br>≥40: 1.18 (1.00–1.38)<br>**Pack-years:**<br>Never: 1.00<br>1–19: 1.05 (0.91–1.21)<br>20–39: 1.18 (1.02–1.37)<br>≥40: 1.15 (0.96–1.37)<br>**Age at Smoking Initiation:**<br>Never: 1.00<br>≤18: 1.12 (0.92–1.36)<br>>18: 1.11 (1.00–1.24)<br>**Timing With First Pregnancy:**<br>Never: 1.00<br>Before: 1.21 (1.07–1.37)<br>After: 1.03 (0.88–1.21) | Controlled for age, education, family history, age at menarche, age at menopause, OC use, HRT, BMI, waist-to-hip ratio, height, BMI at 18 years of age, physical activity, and alcohol; overall risk additionally adjusted for parity and age at birth of first child |

**Table 6.14*S* Continued**

| Study | Design/population | Number of breast cancer events | Data collection/subgroup analyses | Findings for active cigarette smoking | Measures of active cigarette smoking: RR (95% CI) | Confounders |
|---|---|---|---|---|---|---|
| Cui et al. 2006[a] | • Canadian National Breast Screening Study<br>• 89,835 women enrolled from 1980–1985 into a multicenter, randomized controlled trial of mammographic screening<br>• Average follow-up: 16 years<br>• 40–59 years of age<br>• Canada | 4,445 incident cases (in situ, invasive) | • Self-administered questionnaire at enrollment.<br>• Data collected for smoking status (never, former, and current), cigarettes/day, duration, pack-years of smoking<br>• Subgroups evaluated and stratified by levels of physical activity | • Significantly increased risk in current but not former smokers.<br>• Risk significantly associated with duration, cigarettes/day, pack-years of smoking, age at smoking initiation and smoking before first pregnancy<br>• Risk associated with age at smoking initiation but not with number of years since cessation<br>• Significant trends for duration, cigarettes/day, pack-years, age at smoking initiation, and smoking before first pregnancy | **Status:**<br>Never: 1.00<br>Former: 1.00 (0.93–1.08)<br>Current: 1.18 (1.09–1.27)<br>**Duration (Years):**<br>Never: 1.00<br>1–9: 1.00 (0.90–1.12)<br>10–19: 1.02 (0.93–1.13)<br>20–29: 1.09 (1.00–1.19)<br>30–39: 1.14 (1.03–1.27)<br>≥40: 1.50 (1.19–1.89)<br>p trend = 0.0003<br>**Cigarettes/Day:**<br>Never: 1.00<br>1–9: 1.02 (0.92–1.13)<br>10–19: 1.06 (0.96–1.16)<br>20–29: 1.12 (1.03–1.21)<br>30–39: 1.08 (0.92–1.28)<br>≥40: 1.20 (1.00–1.44)<br>p trend = 0.0018<br>**Pack-years:**<br>Never: 1.00<br>1–9: 1.02 (0.93–1.11)<br>10–19: 1.02 (0.92–1.13)<br>20–29: 1.13 (1.02–1.27)<br>30–39: 1.21 (1.07–1.36)<br>≥40: 1.17 (1.02–1.34)<br>p trend = 0.0002<br>**Age at Smoking Initiation:**<br>Never: 1.00<br>≥20: 1.07 (0.99–1.14)<br>16–19: 1.10 (1.01–1.21)<br><16: 1.11 (0.97–1.28)<br>p trend = 0.01<br>**Timing With First Pregnancy: Before (Years)**<br>Never: 1.00<br>>0–5: 1.01 (0.91–1.13)<br>>5: 1.13 (1.01–1.25)<br>p trend = 0.041 | Controlled for age, randomization group (intervention, control), study center, BMI, education, physical activity, OC use, HRT, parity, age at menarche, history of benign breast disease, breast self-exam, family history, menopausal status, and alcohol use |

**Table 6.14*S* Continued**

| Study | Design/population | Number of breast cancer events | Data collection/subgroup analyses | Findings for active cigarette smoking | Measures of active cigarette smoking: RR (95% CI) | Confounders |
|---|---|---|---|---|---|---|
| Ha et al. 2007 | • United States Radiologic Technologists Study<br>• 146,022 women, enrolled in 1983 if registered for at least 2 years between 1926–1982 through the American Registry of Radiologic Technologists to assess lifestyle and health information<br>• Average follow-up: 15 years<br>• Age (mean): 37.5 (22–92) years<br>• United States | 906 incident breast cancer cases (stage not specified)<br>781 cases based on self-report only and 125 cases from death certificates<br>Ascertained from subcohort of 54,222 women with updated data during 1994–1998 and 1,520 women deceased from 1983–1998 | • Self-administered questionnaire at enrollment and at follow-up (1994–1998)<br>• Data collected for smoking status (never, former, and current), number of cigarettes and duration of smoking<br>• Data collected for smoking at 3 reproductive time periods: menopause, age at birth of first birth, and age at menarche<br>• Subgroups evaluated and stratified by menopausal status | • No association with current or former smoking<br>• Trend showing increased risk with earlier age at initiation and with smoking before first pregnancy, but statistically significant in only postmenopausal women | **Status:**<br>Never: 1.00<br>Former: 1.17 (0.99–1.38)<br>Current: 1.13 (0.96–1.32)<br>**Age at Smoking Initiation:**<br>Never: 1.00<br>>20: 0.97 (0.60–1.57)<br>18–20: 1.09 (0.64–1.86)<br>15–17: 1.19 (0.68–2.06)<br><15: 1.48 (0.77–2.84)<br>p trend = 0.06<br>**Age at Smoking Initiation: Premenopausal**<br>Never: 1.00<br>>20: 1.15 (0.47–2.81)<br>18–20: 1.06 (0.39–2.87)<br>15–17: 1.35 (0.49–3.69)<br><15: 0.87 (0.25–3.07)<br>p trend = 0.93<br>**Age at Smoking Initiation: Postmenopausal**<br>Never: 1.00<br>>20: 1.00 (0.55–1.78)<br>18–20: 1.17 (0.61–1.78)<br>15–17: 1.17 (0.60–2.30)<br><15: 2.01 (0.92–4.37)<br>p trend = 0.05<br>**Timing With First Pregnancy: Before (Years)**<br>Never: 1.00<br><10: 0.97 (0.61–1.54)<br>≥10: 1.39 (0.82–2.35)<br>p trend = 0.002<br>**Timing With First Pregnancy: Premenopausal, Before (Years)**<br>Never: 1.00<br><10: 0.81 (0.33–2.00)<br>≥10: 1.38 (0.51–3.73)<br>p trend = 0.12<br>**Timing With First Pregnancy: Postmenopausal, Before (Years)**<br>Never: 1.00<br><10: 1.04 (0.61–1.78)<br>≥10: 1.37 (0.74–2.56)<br>p trend = 0.01 | Controlled for age, birth cohort, alcohol use, age at menarche, age at birth of first live child, parity, family history, HRT, time period working as a radiologic technologist, BMI, and menopausal status |

**Table 6.14*S* Continued**

| Study | Design/population | Number of breast cancer events | Data collection/subgroup analyses | Findings for active cigarette smoking | Measures of active cigarette smoking: RR (95% CI) | Confounders |
|---|---|---|---|---|---|---|
| Lin et al. 2008 | • Collaborative Cohort Study for Evaluation of Cancer Risk<br>• 34,401 women enrolled between 1988–1990 from 24 areas for which incidence data were available to evaluate risk factors for cancer<br>• Average follow-up: 11–13 years<br>• 40–79 years of age<br>• Japan | 208 incident cases (stage not specified) | • Self-administered questionnaire at enrollment<br>• Data collected for smoking status (never, former, and current), age at smoking initiation, cigarettes/day, duration of smoking, and years since cessation<br>• Data collected for secondhand smoke exposure (see Table 6.22*S*)<br>• Subgroups evaluated and stratified by menopausal status but data for postmenopausal women only reported because of insufficient data for premenopausal women | • No association between risk for breast cancer and status or dose of smoking<br>• No association with risk for breast cancer and current smoking in postmenopausal women HR = 1.20, (95%CI; 0.52–2.80)<br>• Use of NA/NP referent group did not alter results (data not shown) | **Status:**<br>Never: 1.00<br>Former: 1.27 (0.46–3.48)<br>Current: 0.67 (0.32–1.38)<br>**Cigarettes/Day:**<br>Never: 1.00<br>0–10: 0.84 (0.34–2.06)<br>>11: 0.55 (0.17–1.75) | Controlled for age, geographic area, BMI, family history, alcohol use, daily walking, age at menarche, age at birth of first child, menopausal status at baseline, parity, and HRT |

**Table 6.14*S* Continued**

| Study | Design/population | Number of breast cancer events | Data collection/subgroup analyses | Findings for active cigarette smoking | Measures of active cigarette smoking: RR (95% CI) | Confounders |
|---|---|---|---|---|---|---|
| Luo et al. 2011b | • Women's Health Initiative Observational Cohort<br>• 93,676 women enrolled in 40 clinical centers (1993–1998) to evaluate major causes of morbidity and mortality<br>• 79,990 women included in the analysis<br>• Average follow-up: 10.3 years<br>• 50–79 years of age<br>• United States | 3,520 incident cases (invasive) | • Self-administered questionnaire at enrollment<br>• Data collected for smoking status (never, former, current), age at initiation, duration, cigarettes/day, pack-years, years since cessation, age at initiation, and before first pregnancy<br>• Data collected for secondhand smoke exposure (See Table 6.22*S*)<br>• Subgroups evaluated and stratified by tumor subgroups, hormone receptor status and histology | • Risk significantly increased in former and current smokers compared to never smokers with slightly higher risk when referent group was based on active/no passive exposure<br>• Significant trends for increased risk with duration, cigarettes/day, pack-years and younger age at initiation<br>• Risk significantly increased with smoking before first pregnancy<br>• Risk of breast cancer was significantly elevated among former and current smokers with ER+/PR+ receptor status (results not shown) | **Status:**<br>Never: 1.00<br>Former: 1.09 (1.02–1.17)<br>Current: 1.16 (1.00–1.34)<br>**Status With NA/NP:**<br>NA/NP: 1.00<br>Former: 1.16 (0.98–1.38)<br>Current: 1.24 (1.00–1.54)<br>**Duration (Years):**<br>Never: 1.00<br><5: 0.97 (0.84–1.11)<br>5–9: 1.05 (0.90–1.22)<br>10–19: 1.09 (0.98–1.22)<br>20–29: 1.09 (0.97–1.22)<br>30–39: 1.21 (1.07–1.36)<br>40–49: 1.14 (0.98–1.34)<br>≥50: 1.35 (1.03–1.77)<br>p-trend: 0.0002<br>**Cigarettes/Day:**<br>Never: 1.00<br><5: 1.05 (0.94–1.17)<br>5–14: 1.11 (1.01–1.23)<br>15–24: 1.14 (1.03–1.27)<br>≥25: 1.08 (0.95–1.22)<br>p trend = 0.01<br>**Pack-years:**<br>Never: 1.00<br><10: 1.04 (0.95–1.14)<br>10–<20: 1.21 (1.08–1.36)<br>20–<30: 1.13 (0.98–1.30)<br>30–<40: 1.01 (0.86–1.19)<br>40–<50: 1.16 (0.91–1.47)<br>≥50: 1.18 (1.02–1.37)<br>p trend = 0.005<br>**Age at Smoking Initiation:**<br>Never: 1.00<br><15: 1.12 (0.92–1.36)<br>15–19: 1.13 (1.04–1.23)<br>20–24: 1.09 (0.99–1.20)<br>25–29: 1.02 (0.84–1.24)<br>≥30: 0.94 (0.75–1.18)<br>p trend = 0.002<br>**Timing With First Pregnancy: Before**<br>Never: 1.00<br>Yes: 1.21 (1.11–1.33)<br>No: 1.12 (0.92–1.36)<br>Uncertain: 1.07 (0.97–1.18) | Controlled for age at enrollment, ethnicity, education, BMI, physical activity, alcohol use, parity, family history, history of HRT, age at menarche, and age of first live birth. |

**Table 6.14*S* Continued**

| Study | Design/population | Number of breast cancer events | Data collection/subgroup analyses | Findings for active cigarette smoking | Measures of active cigarette smoking: RR (95% CI) | Confounders |
|---|---|---|---|---|---|---|
| Xue et al. 2011[a] | • Nurses' Health Study-I<br>• 121,700 nurses enrolled to evaluate risk factors for breast cancer and CVD<br>• Analysis restricted to 111,140 women for active cigarette smoking analysis<br>• Average follow-up: 14 years<br>• 30–55 years of age<br>• United States | 8,772 incident cases (invasive) | • Self-administered questionnaire at enrollment<br>• Data collected for smoking status (never, former, current), cigarettes/day, duration, pack-years, timing in relation to menarche, first birth, and menopause, and time since cessation (former)<br>• Data collected for secondhand smoke exposure (See Table 6.22*S*)<br>• Subgroups evaluated and stratified by menopausal status, passive smoking status, timing of smoking status, and changes in BMI | • Risk significantly increased in ever, former and current smokers<br>• Risk significantly positively associated with cigarettes/day, duration, and pack-years of smoking<br>• Positive association with pack-years of smoking before menopause; inverse association after menopause (results not shown) | **Status:**<br>Never: 1.00<br>Ever: 1.07 (1.02–1.12)<br>Former: 1.06 (1.01–1.11)<br>Current: 1.09 (1.02–1.17)<br>**Duration (Years):**<br>Never: 1.00<br><20: 1.04 (0.98–1.11)<br>20-39: 1.07 (1.00–1.14)<br>≥40: 1.15 (1.04–1.27)<br>p-trend = 0.01<br>**Cigarettes/Day: Current**<br>Never 1.00<br>1–14: 1.04 (0.94–1.15)<br>15–24: 1.06 (0.96–1.17)<br>≥25: 1.14 (1.02–1.29)<br>p trend = 0.02<br>**Cigarettes/Day: Former**<br>Never: 1.00<br>1–14: 1.02 (0.97–1.09)<br>15–24: 1.11 (1.04–1.18)<br>≥25: 1.08 (0.99–1.18)<br>p trend = 0.003<br>**Pack-years:**<br>Never: 1.00<br>1–10: 1.00 (0.94–1.07)<br>11–20: 1.08 (1.01–1.16)<br>21–30: 1.07 (1.00–1.15)<br>31–40 1.16 (1.07–1.26)<br>41–50 1.05 (0.94–1.18)<br>≥50 1.19 (1.07–1.33)<br>p trend = 0.001<br>**Age at Smoking Initiation:**<br>Never:<br>≥20: 1.07 (0.99–1.15)<br>18-19: 1.08 (1.01–1.14)<br>≤17: 1.04 (0.99–1.11)<br>p trend = 0.01 | Controlled for age, family history, age at menarche, height, BMI at 18 years of age, oral contraceptive use, history of benign breast disease, physical activity, alcohol use, passive smoking at home and at work, age at first birth, parity, and current BMI, age at menopause, menopausal status, and HRT use |

**Table 6.14*S* Continued**

*Note:* Study-specific results are not intended to be a complete reporting of all findings. When available, results for ever, status, duration, cigarettes/day, pack-years, age at initiation, and timing with first pregnancy (smoking before or during first pregnancy) are reported. Unless otherwise specified, the definition of the reference group is based on a no active-only exposure, which includes individuals with exposure to secondhand smoke. When available, results for ever smoking using a NA/NP reference group are reported; however, similar results for the other measures are not reported in the table. Data from cohort studies for exposure to secondhand smoke are summarized in Table 6.22*S*. All results reported by the study may not appear in the summary table. **BMI** = body mass index; **cig/day** = cigarettes smoked per day; **CI** = confidence interval; **CVD** = cardiovascular disease; **ER** = estrogen receptor; **HR** = hazard ratio; **HRT** = hormone replacement therapy; **NA/NP** = no active/no passive; **OC** = oral contraceptive; **pack-years** = the number of years of smoking multiplied by the number of packs of cigarettes smoked per day; **PostM** = postmenopausal; **PR** = progesterone receptor; **RR** = relative risk; **USDHHS** = United States Department of Health and Human Services.

[a]Report that overlaps with another from the same study population shown in this table and reported in Table 6.16*S*A.

**Table 6.15*S*** **Case-control study reports of the association between active cigarette smoking and risk for breast cancer, based on studies published from 2000 to 2011 (n = 34)**

| Study | Study population and design | Data collection/subgroup analyses | Findings for active cigarette smoking | Measures of active cigarette smoking RR (95% CI) | Confounders |
|---|---|---|---|---|---|
| Delfino et al. 2000 | • Clinic-based study designed to evaluate the interaction of polymorphisms in the *NAT2* gene with smoking on risk for breast cancer<br>• Time period unknown<br>• >40 years of age<br>• 113 incident cancer cases (in situ, invasive) ascertained through 1 of 3 breast care centers for women evaluated for a suspicious breast mass<br>• 278 controls selected from those with benign breast disease being treated at same clinic as cases<br>• Orange County, California | • Self-administered mailed questionnaire at enrollment; 59 cases excluded from analysis because the questionnaire was received after receipt of diagnosis or refusal of blood draw<br>• Data collected for status (never, former, and current), duration (years), and cigarettes/day<br>• Data collected for exposure to secondhand smoke (see USDHHS 2006)<br>• Assays for *NAT2* genotype<br>• Subgroups evaluated and stratified by type of benign breast disease | • No statistically significant association between risk for breast cancer and any measure of active smoking<br>• No difference when results were stratified by menopausal status (data not reported)<br>• No significant interaction (p >0.30) between active smoking and NAT2 genotype for all women and pre- and postmenopausal women | **Status with NA/NP:**<br>NA/NP: 1.00<br>Passive Only: 1.32 (0.69–2.52)<br>Former: 0.94 (0.53–1.68)<br>Current: 0.55 (0.18–1.67)<br>**Duration (years) with NA/NP:**<br>NA/NP: 1.00<br><13: 0.94 (0.43–2.03)<br>13–26: 0.70 (0.30–1.62)<br>>26: 0.74 (0.34–1.61)<br>**Cigarettes/day with NA/NP:**<br>NA/NP: 1.00<br><8: 1.04 (0.50–2.13)<br>8–25: 0.75 (0.35–1.58)<br>>25: 0.51 (0.19–1.35) | Controlled for age, menopausal status, and family history in first- and second-degree relatives |

**Table 6.15*S* Continued**

| Study | Study population and design | Data collection/subgroup analyses | Findings for active cigarette smoking | Measures of active cigarette smoking RR (95% CI) | Confounders |
|---|---|---|---|---|---|
| Johnson et al. 2000 | • National Enhanced Cancer Surveillance System<br>• Population-based study of cancer risk profiles collected on 19,453 cases diagnosed with 18 different incident cancers and 4,523 controls<br>• Analysis based on data from 8 of 10 provinces<br>• 1994–1997<br>• 25–74 years of age<br>• 2,317 incident cases (invasive) ascertained through tumor registries<br>• 2,438 controls selected randomly from provincial health insurance plans in 5 provinces, databases of the Ministry of Finance Property Assessment in one province, and random-digit dialing in two provinces<br>• Canada | • Self-administered questionnaire at time of enrollment<br>• Data collected for status (never, former, current), pack-years, duration, age at smoking initiation, and years since smoking cessation<br>• Data collected for exposure to secondhand smoke (see USDHHS 2006)<br>• Subgroups evaluated and stratified by menopausal status | • Statistically significant increased risk for breast cancer among former or current (ever) smokers when referent groups is no active/no passive exposure in both pre- and postmenopausal women<br>• Significant trend involving increased risk with greater duration and greater pack-years among postmenopausal but not premenopausal women<br>• Increased risks across all levels of age at smoking initiation with no significant trends | **Status: premenopausal**<br>Never: 1.00<br>Former: 1.20 (0.90–1.50)<br>Current: 0.90 (0.70–1.20)<br>Former or Current: 1.00 (0.80–1.30)<br>**Status: postmenopausal**<br>Never: 1.00<br>Former: 1.10 (0.90–1.30)<br>Current: 1.30 (1.10–1.60)<br>Former or Current: 1.20 (1.00–1.40)<br>**Status with NA/NP: premenopausal**<br>NA/NP: 1.00<br>Passive: 2.30 (1.20–4.60)<br>Former: 2.60 (1.30–5.30)<br>Current: 1.90 (0.90–3.80)<br>Former or Current: 2.30 (1.20–4.50)<br>**Status with NA/NP: postmenopausal**<br>NA/NP: 1.00<br>Passive: 1.20 (0.80–1.80)<br>Former: 1.40 (0.90–2.10)<br>Current: 1.60 (1.00–2.50)<br>Former or Current: 1.50 (1.00–2.30)<br>**Duration (years) with NA/NP: premenopausal**<br>NA/NP: 1.00<br>1–11: 2.70 (1.20–6.10)<br>12–20: 1.90 (0.80–4.50)<br>≥21: 2.10 (0.90–4.70)<br>p trend = 0.91<br>**Duration (years) with NA/NP: postmenopausal**<br>NA/NP: 1.00<br>1–20: 1.20 (0.80–1.90)<br>21–35: 1.30 (0.80–2.10)<br>≥35: 1.70 (1.10–2.70)<br>p trend = 0.003 | Active smoking controlled for 10-year age groups, province, education, BMI, use of alcohol, physical activity, age at menarche, age at end of first pregnancy, number of live births, months breastfeeding, and height; exposure to passive smoke controlled for in analyses that evaluated status of cigarette smoking |

**Table 6.15*S* Continued**

| Study | Study population and design | Data collection/subgroup analyses | Findings for active cigarette smoking | Measures of active cigarette smoking RR (95% CI) | Confounders |
|---|---|---|---|---|---|
| Johnson et al. 2000 (continued) | | | | **Cigarettes/day with NA/NP: premenopausal**<br>NA/NP: 1.00<br><10: 2.50 (1.20–5.20)<br>10–19: 2.30 (1.10–4.60)<br>≥20: 2.00 (1.00–4.00)<br>p trend = 0.99<br>**Cigarettes/day with NA/NP: postmenopausal**<br>NA/NP: 1.00<br><10: 1.40 (0.80–2.20)<br>10–19: 1.50 (0.90–2.30)<br>≥20: 1.40 (0.90–2.10)<br>p trend = 0.08<br>**Pack-years with NA/NP: premenopausal**<br>NA/NP: 1.00<br>1–10: 2.40 (1.20–4.70)<br>11–20: 2.30 (1.10–4.70)<br>21–30: 1.70 (0.80–3.90)<br>>30: 1.50 (0.40–5.90)<br>p trend = 0.92<br>**Pack-years with NA/NP: Ppstmenopausal**<br>NA/NP: 1.00<br>1–10: 1.40 (0.90–2.10)<br>11–20: 1.20 (0.70–1.90)<br>21–30: 1.90 (1.10–3.10)<br>>30: 1.60 (1.00–2.60)<br>p trend = 0.01<br>**Age at smoking initiation with NA/NP: premenopausal**:<br>NA/NP: 1.00<br>≥20: 2.10 (0.90–4.80)<br>16–19: 2.40 (1.20–4.90)<br>≤15: 2.10 (1.00–4.30)<br>p trend = 0.63<br>**Age at smoking initiation with NA/NP: postmenopausal**<br>NA/NP: 1.00<br>≥20: 1.40 (0.90–2.30<br>16–19: 1.50 (1.00–2.40)<br>≤15: 1.20 (0.70–1.90)<br>p trend = 0.19 | |

**Table 6.15*S* Continued**

| Study | Study population and design | Data collection/subgroup analyses | Findings for active cigarette smoking | Measures of active cigarette smoking RR (95% CI) | Confounders |
|---|---|---|---|---|---|
| Marcus et al. 2000[a] | • Carolina Breast Cancer Study (Phase I)<br>• Population-based study designed to evaluate the association between risk of breast cancer and adolescent exposure to cigarette smoking, alcohol use, passive smoke, and ionizing radiation treatment in White and African American women<br>• 1993–1996<br>• 20–74 years of age<br>• 864 incident breast cancer cases (invasive) ascertained by North Carolina Central Cancer Registry<br>• 790 controls frequency-matched by age and residence and selected from North Carolina Division of Motor Vehicles list (<65 years of age) and from Medicare list (>65 years of age)<br>• North Carolina | • Telephone interview or in-person if subject could not be reached by telephone<br>• Data collected for status (never, former, current), age at smoking initiation, and duration.<br>• Data collected for exposure to secondhand smoke (see USDHHS 2006) | • No statistically significant association between active smoking and risk of breast cancer among former and current smokers<br>• Statistically significant increased risk among women who smoked for 20 or more years) | **Status:**<br>Never: 1.00<br>Former: 1.10 (0.80–1.30)<br>Current: 1.20 (0.90–1.50)<br>**Duration (years):**<br>Never: 1.00<br><20: 0.90 (0.70–1.20)<br>≥20: 1.30 (1.10–1.80)<br>**Age at smoking initiation:**<br>Never: 1.00<br>10–14: 1.50 (0.90–2.50)<br>15–19: 1.00 (0.80–1.30)<br>≥20: 1.20 (0.80–1.50) | Controlled for race, age at diagnosis or selection, and sampling design |

**Table 6.15*S* Continued**

| Study | Study population and design | Data collection/subgroup analyses | Findings for active cigarette smoking | Measures of active cigarette smoking RR (95% CI) | Confounders |
|---|---|---|---|---|---|
| Morabia et al. 2000 | • Population-based study designed to evaluate the interaction of smoking and the *NAT2* genotype with risk for breast cancer 1992–1993<br>• 30–74 years of age<br>• 177 incident cases (stage not specified) identified via computerized database of residents in Geneva<br>• 170 controls selected from a computerized database of residents; frequency-matched to cases and proportionate for each 10-year age group<br>• Geneva, Switzerland | • In-person interview data from parent study<br>• Data collected for ever smoking<br>• Data collected for exposure to secondhand smoke (see note for Table 6.24*S*)<br>• Data collection included DNA buccal samples for NAT2 genotyping<br>• Subgroups evaluated and stratified by menopausal status and *NAT2* acetylator status | • Risk for breast cancer was statistically significant and 3-fold higher for ever active smokers. | **Ever with NA/NP:**<br>Never: 1.00<br>Ever: 3.30 (1.70–6.50) | Controlled for age, education, and family history |
| Innes and Byers, 2001 | • Population-based study designed to evaluate whether smoking during pregnancy was associated with an increased risk of breast cancer<br>• 1989–1995<br>• 319 incident cases (invasive) ascertained through the New York State Department of Health Cancer Registry and Vital Statistics Registry if a state resident and gave birth to at least 1 child after 1987<br>• 768 primiparous controls selected from the same registry and vital statistics registry as cases and matched to cases on county of residence and delivery date<br>• 26–45 years of age<br>• New York | • Data abstracted for maternal history of smoking, including smoking during first pregnancy, and for potential confounders available on birth certificate | • Smoking during pregnancy increased risk of breast cancer three-fold<br>• Additional adjustment for use of alcohol during pregnancy, pre-eclampsia, multifetal gestation, and prepregnancy weight further increased RR to 4.8 (1.6–14.6)<br>• Women who were at or above median body weight and smoked were more likely to develop breast cancer (data not provided). | **Status: during first pregnancy**<br>Nonsmoker: 1.00<br>Smoker: 3.00 (1.30–7.20) | Controlled for attained age, age at birth of first child, maternal education, maternal race |

**Table 6.15*S* Continued**

| Study | Study population and design | Data collection/subgroup analyses | Findings for active cigarette smoking | Measures of active cigarette smoking RR (95% CI) | Confounders |
|---|---|---|---|---|---|
| Band et al. 2002 | • Population-based study designed to assess the association between cigarette smoking and breast cancer (based on a previous case-control study that evaluated occupational exposures to cigarette smoke)<br>• 1988–1989<br>• <75 years of age<br>• 1,431 cases (stage not provided) ascertained cases through the British Columbia Cancer Registry; 1,018 cases (68%) included in analyses<br>• From 1,502 eligible controls, selected randomly from a list of provincial voters and matched by age (±5 years); 1,025 controls (67%) included in analyses<br>• British Columbia, Canada | • Self-administered questionnaire at enrollment<br>• Data collected for status (never and ever), duration, pack-years of smoking, and cigarettes/day, timing with respect to menarche, first pregnancy, and first full-term pregnancy<br>• Subgroups evaluated and stratified by menopausal status, BMI, and parity | • Statistically significant increased risk for breast cancer with ever smoking and for duration, pack-years of smoking, and cigarettes/day for premenopausal women only | **Ever: premenopausal**<br>Never: 1.00<br>Ever: 1.50 (1.09–2.07)<br>**Ever: postmenopausal**<br>Never: 1.00<br>Ever: 0.96 (0.77–1.19)<br>**Duration (Years): Premenopausal**<br>Never: 1.00<br><20: 1.34 (0.91–1.99)<br>≥20: 1.60 (1.08–2.37)<br>**Duration (years): postmenopausal**<br>Never: 1.00<br><20: 0.77 (0.54–1.08)<br>≥20: 1.01 (0.80–1.28)<br>**Cigarettes/day: premenopausal**<br>Never: 1.00<br><20: 1.37 (0.94–2.01)<br>≥20: 1.58 (1.06–2.37)<br>**Cigarettes/day: postmenopausal**<br>Never: 1.00<br><20: 0.93 (0.72–1.18)<br>≥20: 1.02 (0.76–1.36)<br>**Pack-years: premenopausal**<br>Never: 1.00<br><20: 1.30 (0.90–1.87)<br>≥20: 1.69 (1.10–2.61)<br>**Pack-years: postmenopausal**<br>Never: 1.00<br><20: 0.84 (0.64–1.09)<br>≥20: 1.03 (0.79–1.34)<br>**Timing with first pregnancy: premenopausal**<br>Never: 1.00<br>Before: 1.51 (1.07–2.13)<br>After: 0.83 (0.38–1.86)<br>**Timing with first pregnancy: postmenopausal**<br>Never: 1.00<br>Before: 0.97 (0.77–1.23)<br>After: 0.63 (0.41–0.96) | Controlled for age only in final model; multiple covariates were available and tested for confounding including: ethnicity, marital status, education, use of alcohol, ages at menarche and menopause, family history, history of benign breast disease, body size, use of oral contraceptives, HRT, number of pregnancies and live births, age at first pregnancy, age at first full-term birth and breastfeeding |

**Table 6.15*S* Continued**

| Study | Study population and design | Data collection/subgroup analyses | Findings for active cigarette smoking | Measures of active cigarette smoking RR (95% CI) | Confounders |
|---|---|---|---|---|---|
| Kropp and Chang-Claude 2002 | • Population-based study designed to assess risk factors for breast cancer<br>• 1992–1995<br>• <51 years of age<br>• 468 incident cases (in situ, invasive) ascertained through hospital admission records<br>• 1,093 controls selected randomly from population registries and matched (2:1) to cases by age and study region<br>• 2 regions in southern Germany | • Self-administered questionnaire at enrollment<br>• Data collected for status (never, former, and current), age at initiation, duration, cigarettes/day, type of tobacco product, intensity of inhalation, cessation, and changes in smoking<br>• Data collected for exposure to secondhand smoke and categorized into low and high passive exposure categories (see USDHHS 2006)<br>• Subgroups evaluated for joint effects of active and passive smoking | • Increased risk for breast cancer for ever smokers and current smokers<br>• Significant trend of increased risk for long duration of smoking and for age at smoking initiation<br>• No association between risk and smoking before first pregnancy | **Status with NA/NP:**<br>NA/NP: 1.00<br>Passive only: 1.61 (1.08–2.39)<br>Ever: 1.31 (0.90–1.92)<br>Former: 1.15 (0.76–1.74)<br>Current: 1.47 (0.99–2.20)<br>**Status with NA/NP: current smoker**<br>NA/NP: 1.00<br>Active: 1.11 (0.63–1.96)<br>Low Passive: 1.06 (0.69–1.64)<br>High Passive: 1.46 (0.97–2.18)<br>**Duration (years) with NA/NP:**<br>NA/NP: 1.00<br>1–9: 0.99 (0.61–1.60)<br>10–19: 1.40 (0.90–2.16)<br>≥20: 1.45 (0.96–2.19)<br>p trend = 0.047<br>**Pack-years with NA/NP:**<br>NA/NP: 1.00<br>≤10: 1.19 (0.80–1.76)<br>11–20: 1.84 (1.17–2.88)<br>≥20: 1.13 (0.68–1.88)<br>p trend = 0.211<br>**Age at smoking initiation with NA/NP:**<br>NA/NP: 1.00<br>9–15: 1.02 (0.62–1.68)<br>16–18: 1.29 (0.86–1.94)<br>≥19: 1.54 (0.99–2.37)<br>p trend = 0.015<br>**Timing with first pregnancy with NA/NP:**<br>NA/NP: 1.00<br>Before: 0.92 (0.52–1.65)<br>After: 1.64 (0.90–2.97)<br>Before and After: 1.32 (0.86–2.03) | Controlled for average daily alcohol use, months breastfeeding, education, family history, menopausal status, and BMI; category of exposure to only passive smoke included in all models |

**Table 6.15*S* Continued**

| Study | Study population and design | Data collection/subgroup analyses | Findings for active cigarette smoking | Measures of active cigarette smoking RR (95% CI) | Confounders |
|---|---|---|---|---|---|
| Lash and Aschengrau 2002 | • Population-based study designed to evaluate the effect of active smoking and exposure to passive smoke on risk for breast cancer<br>• 1987–1993<br>• Age criteria unknown<br>• 666 incident cases (invasive) identified through Massachusetts Cancer Registry for eight towns on Cape Cod<br>• 615 controls, matched to cases by age and vital status, selected by random-digit dialing (<65 years of age) and from Medicare beneficiaries (≥65 years of age)<br>• Massachusetts | • Mixture of in-person and telephone interviews for study participants or their proxies<br>• Information was not provided on the number of proxy interviews or the source of the information<br>• Data collected for status (never and ever), duration, packs/day, age at smoking initiation, and in relation to first pregnancy<br>• Data collected for exposure to secondhand smoke (see USDHHS 2006) | • No statistically significant association between the risk for breast cancer and any measure of active smoking<br>• Statistically significant inverse association for ever smoking and a nonsignificant inverse association for all other measures | **Status with NA/NP:**<br>NA/NP: 1.00<br>Ever: 0.72 (0.55–0.95)<br>**Duration (Years) with NA/NP:**<br>NA/NP: 1.00<br><20: 0.69 (0.48–1.00)<br>20–40: 0.87 (0.74–1.00)<br>≥40: 0.90 (1.80–1.00)<br>p trend = 0.87<br>**Packs/day with NA/NP:**<br>NA/NP: 1.00<br><1: 0.77 (0.57–1.00)<br>1–2: 0.69 (0.50–0.94)<br>≥2: 0.57 (0.33–0.98)<br>p trend = 0.40<br>**Age at smoking initiation with NA/NP:**<br>NA/NP: 1.00<br><13: 0.61 (0.30–1.20)<br>14–15: 0.81 (0.54–1.20)<br>16–17: 0.67 (0.47–1.00)<br>18–21: 0.78 (0.57–1.10)<br>21–29: 0.71 (0.47–1.10)<br>≥30: 0.59 (0.32–1.10)<br>p trend = 0.81<br>**Timing with first pregnancy with NA/NP:**<br>NA/NP: 1.00<br>Before: 0.73 (0.42–1.30)<br>After: 0.66 (0.42–1.00)<br>Before and After: 0.69 (0.49–0.96)<br>Nulliparous: 0.82 (0.48–1.40) | Controlled for history of medical radiation therapy, BMI, family history, history of benign breast disease, alcohol use, age at first birth, and parity |

**Table 6.15*S* Continued**

| Study | Study population and design | Data collection/subgroup analyses | Findings for active cigarette smoking | Measures of active cigarette smoking RR (95% CI) | Confounders |
|---|---|---|---|---|---|
| Zheng et al. 2002a | • Hospital-based study designed to evaluate the association of GSTs with risk of breast cancer and to determine if they modify the relationship between selected environmental factors and risk for breast cancer<br>• 1994–1998<br>• 30–80 years of age<br>• 338 incident cases (invasive) ascertained through Yale–New Haven Hospital<br>• 345 controls frequency-matched to cases by age (5-year intervals) and selected through Yale–New Haven Hospital in clinic for breast-related surgery but with no histological confirmation of breast cancer<br>• Connecticut | • In-person interview<br>• Data collected for status (never, ever, former, and current), age at smoking initiation, duration, pack-years of smoking, and cigarettes/day<br>• Subgroups evaluated and stratified by menopausal status *GSTM1A/B* and *GSTT1* | • No statistically significant association between risk for breast cancer and ever smoking, duration, pack-years, and cigarettes/day, or age at initiation<br>• No difference when stratified by menopausal status<br>• Possible modification of the risk of smoking by GSTT1 genotype in postmenopausal women | **Status:**<br>Never: 1.00<br>Ever: 1.10 (0.80–1.50)<br>Former: 1.10 (0.80–1.60)<br>Current: 1.00 (0.60–1.60)<br>**Duration (years):**<br>Never: 1.00<br><15: 0.90 (0.60–1.40)<br>15–30: 1.10 (0.70–1.60)<br>>30: 1.30 (0.80–2.00)<br>**Pack-years:**<br>Never: 1.00<br><5: 1.00 (0.70–1.60)<br>5–20: 1.20 (0.80–1.80)<br>>20: 1.00 (0.60–1.50)<br>**Cigarettes/day:**<br>Never 1.00<br><10: 1.20 (0.80–1.80)<br>10–20: 1.10 (0.80–1.60)<br>>20: 0.80 (0.40–1.50)<br>**Age at smoking initiation:**<br>Never: 1.00<br><18: 1.10 (0.80–1.60)<br>18–24: 1.00 (0.70–1.50)<br>>24: 1.60 (0.70–3.70) | Controlled for age, BMI, age at first full-term pregnancy, breastfeeding, and family history of breast cancer |

**Table 6.15*S* Continued**

| Study | Study population and design | Data collection/subgroup analyses | Findings for active cigarette smoking | Measures of active cigarette smoking RR (95% CI) | Confounders |
|---|---|---|---|---|---|
| Egan et al. 2003[a] | • Collaborative Breast Cancer Study<br>• Population-based study designed to investigate factors related to breast cancer<br>• 1997–1998<br>• 20–69 years of age<br>• 791 incident cases (invasive) ascertained through state cancer registries<br>• 797 controls selected randomly within age strata from driver's license lists (<65 years of age) and Medicare beneficiaries lists (>65 years of age)<br>• Massachusetts and Wisconsin | • Telephone interview<br>• Data collected for status (never, former, and current), age at smoking initiation, duration, and timing with first full-term pregnancy<br>• DNA buccal specimens collected by mail for *NAT2* genotyping<br>• Subgroups evaluated and stratified by menopausal status and *NAT2* acetylation type (fast/slow) | • Statistically significant increased risk for breast cancer among ever smokers<br>• Nonsignificant increased risk for women who initiated smoking at or before 16 years of age<br>• No difference in risk by menopausal status for the highest dose category of pack-years of smoking and statistically significant for only postmenopausal women | **Ever:**<br>Never: 1.00<br>Ever: 1.37 (1.12–1.69)<br>**Pack-years: premenopausal**<br>≤25: 0.90 (0.87–1.33)<br>>25: 1.54 (0.87–2.71)<br>p trend = 0.11<br>**Pack-years: postmenopausal:**<br>≤25: 1.57 (1.12–2.19)<br>>25: 1.53 (1.10–2.13)<br>p trend = 0.02<br>**Age at smoking initiation:**<br>≤16: 1.23 (0.83–1.83)<br>>16: 1.19 (0.86–1.66) | Controlled for state, age, education, age at menarche, parity, age at first birth, benign breast disease, recent BMI, family history, age at menopause, and alcohol use |

**Table 6.15*S* Continued**

| Study | Study population and design | Data collection/subgroup analyses | Findings for active cigarette smoking | Measures of active cigarette smoking RR (95% CI) | Confounders |
|---|---|---|---|---|---|
| Fink and Lash 2003 | • Population-based study designed to evaluate whether smoking during pregnancy is associated with an increased risk for breast cancer<br>• 1987–1999<br>• 25–55 years of age<br>• 1,665 cases (invasive) ascertained through linkage of Massachusetts Cancer Registry and Registry of Vital Records for women who were state residents and gave birth to at least 1 child<br>• 4,972 controls selected from the Registry of Vital ecords and matched to cases (3:1) on age (±6 months), year of giving birth, and birth facility<br>• Massachusetts | • Data abstracted for maternal history of smoking, including smoking during first pregnancy, duration, and intensity of smoking and for potential confounders available on birth certificates<br>• Subgroups evaluated and stratified by age at birth of first child for smokers and nonsmokers | • No association between risk for breast cancer and smoking during pregnancy | **Status: during first pregnancy**<br>Nonsmoker: 1.00<br>During: 0.97 (0.80–1.20)<br>**Cigarettes/day: during first pregnancy**<br>Nonsmoker: 1.00<br>Any: 1.00 (0.81–1.20)<br>1–10: 0.94 (0.73–1.20)<br>≥11: 1.00 (0.79–1.40)<br>**Age at first pregnancy:**<br>Nonsmoker: 1.00<br>All Women: 0.90 (0.66–1.20)<br><30: 1.10 (0.65–1.80)<br>30–34: 0.72 (0.43–1.20)<br>≥35: 0.90 (0.49–1.70) | Controlled for age, year of birth, parity, birth terminations (miscarriage, abortions, stillbirths), race, mother and father's education |

**Table 6.15*S* Continued**

| Study | Study population and design | Data collection/subgroup analyses | Findings for active cigarette smoking | Measures of active cigarette smoking RR (95% CI) | Confounders |
|---|---|---|---|---|---|
| van der Hel et al. 2003b | • Monitoring Project on Cardiovascular Disease Risk Factors<br>• Nested case-control study of a population-based sample of >36,000 women and men enrolled from municipal registries to investigate risk factors associated with CVD<br>• 1987–1991<br>• 20–59 years of ages<br>• 229 first incident cases (invasive) identified at follow-up via Netherlands Cancer Registry<br>• 264 controls frequency-matched on age (5-year groups), menopausal status and residence<br>• The Netherlands | • Self-administered questionnaire at enrollment<br>• Data collected for status (never, former, and current) and duration (years) and intensity of smoking<br>• Assays for *NAT1, NAT2, GSTM1,* and *GSTT1* genotypes<br>• Subgroups evaluated and stratified by menopausal status for cigarettes/day and by genotype | • Nonsignificant increase in risk for breast cancer among ever smokers for cigarettes/day and duration<br>• Statistically significant increased risk (OR = 2.17, 95% CI, 1.04–4.51 for postmenopausal women at the highest category of exposure for cigarettes/day (≥20) | **Duration (years):**<br>Never: 1.00<br><15: 1.22 (0.68–2.18)<br>15–30: 1.37 (0.86–2.16)<br>≥30: 1.55 (0.92–2.61)<br>p trend = 0.07<br>**Cigarettes/day:**<br>Never: 1.00<br><10: 1.22 (0.72–2.06)<br>10–20: 1.37 (0.86–2.18)<br>≥20: 1.55 (0.94–2.54)<br>p trend = 0.06 | Controlled for age, menopausal status, and residence |

**Table 6.15*S* Continued**

| Study | Study population and design | Data collection/subgroup analyses | Findings for active cigarette smoking | Measures of active cigarette smoking RR (95% CI) | Confounders |
|---|---|---|---|---|---|
| Alberg et al. 2004 | • Nested case-control study to evaluate *NAT2* genotype and cigarette smoking on breast cancer risk within the Campaign against Cancer and Heart Disease II cohort designed to evaluate cancer and heart disease in 14,625 women<br>• 1989 baseline<br>• Mean age: 60 years<br>• 115 incident cases (stage not specified) ascertained from Washington County Cancer Registry and Washington County Hospital (for those who were deceased)<br>• 115 controls matched on age (±1 year), race, menopausal status, and date of blood collection<br>• Washington County, Maryland | • In-person interview and blood collection<br>• Self-administered questionnaire at follow-up in 1995<br>• Data collected for smoking status (never, former, and current), duration, and intensity of smoking<br>• Data collected for exposure to secondhand smoke (see Table 6.23*S*)<br>• Subgroups evaluated and stratified by menopausal status and NAT2 acetylator status | • No significant association between former and current smoking and risk of breast cancer<br>• Nonsignificant increased risk with increasing pack-years | **Status:**<br>Never: 1.00<br>Former: 1.10 (0.56–2.10)<br>Current: 0.66 (0.30–1.40)<br>**Status with NA/NP:**<br>NA/NP: 1.00<br>Passive: 1.20 (0.59–2.40)<br>Active: 1.40 (0.70–2.90)<br>p trend = 0.45<br>**Pack-years:**<br>Never: 1.00<br>0.1–15: 1.40 (0.58–3.40)<br>16–82.5: 1.70 (0.70–4.20)<br>p trend = 0.26 | Controlled for age and menopausal status |

**Table 6.15*S* Continued**

| Study | Study population and design | Data collection/subgroup analyses | Findings for active cigarette smoking | Measures of active cigarette smoking RR (95% CI) | Confounders |
|---|---|---|---|---|---|
| Gammon et al. 2004a[a] | • Long Island Breast Cancer Study Project<br>• Population-based study to evaluate environmental risk factors for breast cancer<br>• 1996–1997<br>• 24–98 years of age<br>• 1,356 incident cases (in situ, invasive) identified through 31 pathology departments<br>• 1,383 controls frequency-matched to cases by age (±5 years) and selected through random-digit dialing (<65 years of age) and from rosters of the Health Care Financing Administration (≥65 years)<br>• Nassau and Suffolk counties, New York | • In-person interview<br>• Data collected for status (never, former, and current), duration, cigarettes/day, pack-years of smoking, and timing with first pregnancy<br>• Data collected for exposure to secondhand smoke (see USDHHS 2006)<br>• Subgroups evaluated and stratified by menopausal status, BMI, use of alcohol, hormone replacement therapy, use of oral contraceptives, and family history, and ER/PR status | • No statistically significant association between risk for breast cancer and any measure of active smoking<br>• Increased risk for women exposed to active smoking and to passive smoke who had ER+/PR+ tumors OR = 1.42 (1.00–2.00) | **Ever with NA/NP:**<br>NA/NP: 1.00<br>Passive: 1.04 (0.81–1.35)<br>Active: 1.06 (0.76–1.48)<br>Active and Passive: 1.15 (0.90–1.48)<br>**Ever with NA/NP: premenopausal**<br>NA/NP: 1.00<br>Passive: 1.21 (0.78–1.90)<br>Active: 0.98 (0.54–1.78)<br>Active and Passive: 1.43 (0.93–2.21)<br>**Ever with NA/NP: postmenopausal**<br>NA/NP: 1.00<br>Passive: 0.93 (0.68–1.29)<br>Active: 1.08 (0.72–1.62)<br>Active and Passive: 1.02 (0.74–1.38)<br>**Cigarettes/day with NA/NP: current smokers**<br>NA/NP: 1.00<br>1–9: 1.38 (0.86–2.23)<br>10–19: 1.30 (0.84–2.00)<br>>20: 1.31 (0.94–1.82)<br>**Pack-years with NA/NP: current smokers:**<br>NA/NP: 1.00<br><20: 1.41 (0.95–2.08)<br>>20: 1.33 (0.97–1.83)<br>**Age at smoking initiation with NA/NP:**<br>NA/NP: 1.00<br>Before 18: 0.66 (0.49–0.90)<br>**Timing with first pregnancy with NA/NP:**<br>NA/NP: 1.00<br>Before: 0.72 (0.49–1.05)<br>After: 1.20 (0.76–1.89)<br>Before and After: 1.08 (0.82–1.43) | Controlled for age, history of benign breast disease, BMI at age 20, family history of breast cancer, history of fertility problems, number of pregnancies, menopausal status, and weight in year before reference date |

**Table 6.15*S* Continued**

| Study | Study population and design | Data collection/subgroup analyses | Findings for active cigarette smoking | Measures of active cigarette smoking RR (95% CI) | Confounders |
|---|---|---|---|---|---|
| Li et al. 2005 | • Population-based study designed to examine the association between hormone replacement therapy and risk for breast cancer among older women<br>• 1997–1999<br>• 65–79 years of age<br>• 975 incident cases (invasive) ascertained through the Cancer Surveillance System<br>• 1,007 controls selected from records from the Health Care Financing Administration and matched on age (±5 years)<br>• Washington state | • In-person interview<br>• Data collected for status (never, ever, former, and current), duration, pack-years of smoking, and timing with first full-term pregnancy<br>• Subgroups evaluated and stratified by alcohol use, HRT, and ER/PR status | • Statistically significant increased risk for breast cancer among ever smokers former and current smokers<br>• Risk statistically significant for increased pack-years<br>• Risk statistically significant for women who initiated smoking before the age of 20 ($p < 0.05$); trend across levels also statistically significant ($p<0.05$)<br>• Alcohol use reported to be a significant confounder, but not an effect modifier<br>• Possible interaction between smoking and hormone replacement therapy | **Status:**<br>Never: 1.00<br>Ever: 1.30 (1.00–1.50)<br>Former: 1.20 (1.00–1.50)<br>Current: 1.40 (1.00–1.90)<br>**Duration (years):**<br>Never: 1.00<br><20: 1.00 (0.80–1.40)<br>20–39: 1.30 (1.00–1.70)<br>≥40: 1.40 (1.10–1.70)<br>p trend = 0.006<br>**Cigarettes/day:**<br>Never: 1.00<br><10: 1.30 (1.00–1.70)<br>10–19: 1.30 (1.00–1.70)<br>≥20: 1.20 (0.90–1.50)<br>p trend = 0.057<br>**Pack-years:**<br>Never: 1.00<br><11: 1.00 (0.70–1.30)<br>11–27: 1.40 (1.10–1.90)<br>28–52: 1.30 (1.00–1.80)<br>≥53: 1.30 (1.00–1.70)<br>p trend = 0.009<br>**Age at smoking initiation:**<br>Never: 1.00<br>≥20: 1.20 (1.00–1.60)<br><20: 1.30 (1.00–1.60)<br>p trend = 0.028<br>**Timing with first pregnancy:**<br>Never: 1.00<br>Before: 1.30 (1.00–1.60)<br>After: 1.10 (0.80–1.50) | Controlled for age, reference year, BMI, alcohol use, and HRT |

**Table 6.15*S* Continued**

| Study | Study population and design | Data collection/subgroup analyses | Findings for active cigarette smoking | Measures of active cigarette smoking RR (95% CI) | Confounders |
|---|---|---|---|---|---|
| Metsola et al. 2005[a] | • Hospital-based study designed to evaluate the main effects for genotypes and to examine the effects of these genotypes on modification of other risk factors for breast cancer (e.g., smoking)<br>• 1990–1995<br>• 37–92 years of age<br>• 483 cases (invasive) referred to Kuopio University Hospital<br>• 488 controls randomly selected from same area as cases using Finnish Population Register Centre<br>• Finland | • In-person interviews<br>• Data collected for cigarettes/day (with/without filter), duration, and time since smoking cessation (among women who smoked daily for more than 3 months)<br>• Data collected for exposure to secondhand smoke (see Table 6.23*S*)<br>• Genotype assays for DNA repair genes (*XRCC1* and *XPD*)<br>• Subgroups evaluated and stratified by DNA repair genes | • No significant association between ever smoking and risk for breast cancer<br>• Results evaluated for main effects of genotypes by smoking status but not for modification of effects of smoking by genotypes | **Pack-years with NA/NP:**<br>NA/NP: 1.00<br>Ever: 0.91 (0.65–1.28)<br><5: 0.75 (0.48–1.16)<br>≥5: 1.08 (0.72–1.62) | Controlled for age |
| Sillanpaa et al. 2005a[a] | • Hospital-based study designed to evaluate the main effects for genotypes and to examine the effects of these genotypes on modification of other risk factors for breast cancer (e.g., smoking)<br>• 1990–1995<br>• 37–92 years of age<br>• 483 cases (invasive) referred to Kuopio University Hospital<br>• 488 controls randomly selected from same area as cases using Finnish Population Register Centre with no evidence for previous or current breast problems<br>• Finland | • In-person interviews<br>• Data collected on status (never, former, current), cigarettes/day, duration (years), and time since cessation<br>• Data collected for exposure to secondhand smoke (see Table 6.23*S*)<br>• Genotype assays for *NAT2*<br>• Subgroups evaluated and stratified by *NAT2* | • No significant associations found between smoking status, pack-years, and risk of breast cancer<br>• Results evaluated for main effects of genotypes by smoking status but not for modification of effects of smoking by genotypes | **Status with NA/NP:**<br>NA/NP: 1.00<br>Former: 0.87 (0.56–1.37)<br>Current: 1.34 (0.86–2.09)<br>**Pack-years with NA/NP:**<br>NA/NP: 1.00<br><5: 0.88 (0.55–1.41)<br>≥5: 1.23 (0.80–1.90) | Controlled for age, age at menarche, age at first full-term pregnancy, number of pregnancies, family history, history of benign breast disease, and alcohol use |

**Table 6.15*S* Continued**

| Study | Study population and design | Data collection/subgroup analyses | Findings for active cigarette smoking | Measures of active cigarette smoking RR (95% CI) | Confounders |
|---|---|---|---|---|---|
| Lissowska et al. 2006 | • Population-based study designed to evaluate risk factors for breast cancer<br>• 2000–2003<br>• 20–74 years of age<br>• 2,386 incident cases (in situ, invasive) ascertained from 5 participating hospitals that covered 90% of both cities, supplemented by cancer registry<br>• 2,502 controls randomly selected from Polish electronic database for residents of Poland and matched on city and by 5-year age groups<br>• Warsaw and Lodz, Poland | • In-person interview<br>• Data collected for status (never, ever, former, and current), age at initiation, duration, cigarettes/day, and smoking before and after first full-term pregnancy<br>• Hormone receptor data abstracted from medical records<br>• Genotype assays for NAT2<br>• Data collected for exposure to secondhand smoke (see Table 6.23*S*)<br>• Subgroups evaluated and stratified by age group, ER status and NAT2 acetylation status | • For all women and for women ≥45 years of age there were few statistically significant associations and no significant trends for ever smoking, age at smoking initiation, duration, and cigarettes/day or in relation to birth of first child<br>• Significant associations among women <45 years of age for ever and current smoking, a combination of active and passive exposure; age at initiation <24 years but no significant trend, and for smoking before or after first full-term pregnancy<br>• Statistically significant increased trend for women <45 years of age for duration and for cigarettes/day<br>• Exclusion of women with exposure to passive smoke slightly increased results<br>• Statistically significant increased risks for both smoking before and after first full-term pregnancy and ER+ tumor status for all women (OR = 1.25, 1.04–1.50)<br>• Increased risk in premenopausal women <45 years of age with NAT2 slow phenotype | **Ever with NA/NP:**<br>NA/NP: 1.00<br>Active: 1.23 (0.83–1.83)<br>Active and Passive: 1.21 (0.93–1.59)<br>**Ever with NA/NP: women <45 years**<br>NA/NP: 1.00<br>Active: 1.28 (0.52–3.11)<br>Active and Passive: 2.40 (1.00–5.72)<br>**Status:**<br>Never: 1.00<br>Ever: 1.10 (0.97–1.24)<br>Former: 1.09 (0.93–1.29)<br>Current: 1.12 (0.97–1.29)<br>**Status: women <45 years**<br>Never: 1.00<br>Ever: 1.95 (1.38–2.76)<br>Former: 1.63 (0.97–2.72)<br>Current: 2.03 (1.40–2.95)<br>**Duration (years):**<br>Never: 1.00<br><10: 1.04 (0.85–1.29)<br>10–20: 1.06 (0.85–1.32)<br>>20: 0.99 (0.83–1.20)<br>p trend = 0.86<br>**Duration (years): women <45 years**<br>Never: 1.00<br><10: 1.57 (1.01–2.44)<br>10–20: 1.83 (1.15–2.91)<br>>20: 2.33 (1.32–4.13)<br>p trend = 0.04<br>**Cigarettes/day:**<br>Never: 1.00<br><10: 1.06 (0.86–1.31)<br>10–14: 1.17 (0.97–1.43)<br>>14: 0.99 (0.83–1.20)<br>p trend = 0.42 | Controlled for age, site, education, age at menarche, number of full-term births, age at first full-term birth, age at menopause, BMI, family history, prior benign breast biopsy, previous screening mammography, OC, and HRT |

**Table 6.15*S* Continued**

| Study | Study population and design | Data collection/subgroup analyses | Findings for active cigarette smoking | Measures of active cigarette smoking RR (95% CI) | Confounders |
|---|---|---|---|---|---|
| Lissowska et al. 2006 (continued) | | | | **Cigarettes/day: women <45 years**<br>Never: 1.00<br><10: 2.02 (1.26–3.27)<br>10–14: 2.49 (1.53–4.04)<br>>14: 1.35 (0.83–2.19)<br>p trend = 0.05<br>**Age at smoking initiation:**<br>Never: 1.00<br><17: 1.07 (0.80–1.42)<br>17–19: 1.23 (1.04–1.46)<br>20–24: 1.03 (0.87–1.21)<br>>24: 1.10 (0.90–1.34)<br>**Age at smoking initiation: women <45 years**<br>Never: 1.00<br><17: 1.96 (1.08–3.56)<br>17–19: 2.19 (1.42–3.39)<br>20–24: 1.77 (1.13–2.78)<br>>24: 1.86 (0.79–4.26)<br>p trend = 0.60<br>**Timing with first pregnancy:**<br>Never: 1.00<br>After: 1.06 (0.87–1.29)<br>Before: 1.14 (0.98–1.32)<br>**Timing with first pregnancy: women <45 years**<br>Never: 1.00<br>After: 2.40 (1.27–4.53)<br>Before: 2.03 (1.40–2.94) | |

**Table 6.15*S* Continued**

| Study | Study population and design | Data collection/subgroup analyses | Findings for active cigarette smoking | Measures of active cigarette smoking RR (95% CI) | Confounders |
|---|---|---|---|---|---|
| Mechanic et al. 2006[a] | • Carolina Breast Cancer Study<br>• Population-based study designed to evaluate causes of breast cancer among African American and White women (Phase I invasive; Phase II in-situ)<br>• 1993–2001<br>• 20–74 years of age<br>• 2,308 incident cases (in situ, invasive) ascertained through North Carolina Cancer Registry for counties in central and eastern North Carolina<br>• 2,022 controls selected from lists provided by the North Carolina Division of Motor Vehicles for women younger than 65 years of age and from records of the United States Health Care Financing Administration (65–74 years of age)<br>• North Carolina | • In-person interview<br>• Data collected for status (never, former, and current), age at smoking initiation, duration, packs/day, and time since smoking cessation<br>• Clinical data collected from medical records<br>• Genotype assays for polymorphisms in nucleotide excision repair genes<br>• Data collected for exposure to secondhand smoke (see Table 6.23*S*)<br>• Subgroups evaluated and stratified by menopausal status, ethnicity, nucleotide excision repair polymorphisms and alcohol use (data not provided) | • Risk for breast cancer significantly associated with age at smoking initiation, duration, and packs/day for only African American women<br>• Risk significantly associated with status, duration, and packs/day for African American women with ≥4 at risk genotypes | **Status: african american**<br>NA/NP: 1.00<br>Former: 1.80 (1.30–2.50)<br>Current: 1.20 (0.90–1.70)<br>**Status: white**<br>NA/NP: 1.00<br>Former: 1.20 (0.90–1.50)<br>Current: 0.80 (0.60–1.00)<br>**Duration (Years): african american**<br>NA/NP: 1.00<br>≤10: 1.30 (0.90–1.90)<br>11–20: 1.40 (1.00–2.10)<br>>20: 1.80 (1.20–2.60)<br>p trend = 0.003<br>**Duration (years): white**<br>NA/NP: 1.00<br>≤10: 0.90 (0.70–1.20)<br>11–20: 0.90 (0.70–1.30)<br>>20: 1.10 (0.90–1.50)<br>p trend = 0.43<br>**Packs/day: african american**<br>NA/NP: 1.00<br><0.5: 1.50 (1.00–2.00)<br>0.5–1: 1.70 (1.20–2.40)<br>>1: 1.50 (0.90–2.30)<br>p trend = 0.02<br>**Packs/day: white**<br>NA/NP: 1.00<br><0.5: 0.90 (0.70–1.20)<br>0.5–1: 1.00 (0.80–1.30)<br>>1: 1.10 (0.80–1.40)<br>**Age at smoking initiation: african american**<br>NA/NP: 1.00<br><18: 1.50 (1.10–2.20)<br>≥18: 1.50 (1.10–2.10)<br>**Age at smoking initiation: white**<br>NA/NP: 1.00<br><18: 0.90 (0.70–1.20)<br>≥18: 1.10 (0.80–1.40) | Controlled for age, age at menarche, age at first full-term birth, parity, family history, and alcohol use |

**Table 6.15*S* Continued**

| Study | Study population and design | Data collection/subgroup analyses | Findings for active cigarette smoking | Measures of active cigarette smoking RR (95% CI) | Confounders |
|---|---|---|---|---|---|
| Kruk 2007 | • Hospital-based study designed to evaluate the association between the risk for breast cancer risk and lifestyle factors by menopausal status<br>• 2003–2007<br>• 28–78 years of age<br>• 858 incident cases (invasive) ascertained from Szczecin Regional Cancer Registry<br>• 1,085 controls frequency-matched on 5-year age groups and place of residence (urban/rural); majority of controls (79%) from the same patient clinic and remainder from hospital patients<br>• Western Pomerania region, Poland | • Self-administered questionnaire<br>• Data collected for smoking status (never and ever) and cigarettes/day<br>• Data collected for exposure to secondhand smoke (see Table 6.23*S*)<br>• Subgroups evaluated and stratified by menopausal status for cigarettes/day | • Risk for breast cancer significantly associated with smoking, regardless of menopausal status | **Cigarettes/day: premenopausal**<br>Never: 1.00<br><10: 2.09 (1.42–3.09)<br>>10: 2.55 (1.81–3.60)<br>p trend <0.0001<br>**Cigarettes/day: postmenopausal**<br>Never: 1.00<br><10: 1.73 (1.23–2.44)<br>>10: 1.78 (1.33–2.37)<br>p trend <0.0001 | Controlled for age; final models included confounders that influenced goodness of fit and that were statistically significant for risk of breast cancer |

**Table 6.15*S* Continued**

| Study | Study population and design | Data collection/subgroup analyses | Findings for active cigarette smoking | Measures of active cigarette smoking RR (95% CI) | Confounders |
|---|---|---|---|---|---|
| Magnusson et al. 2007 | • Population-based study designed to evaluate the association between smoking and breast cancer<br>• 1993–1995<br>• 50–74 years of age<br>• 3,345 cases (invasive) ascertained through the Regional Cancer Registries<br>• 3,454 controls, randomly selected using registry of the total population, and frequency-matched on 5-year age groups<br>• Sweden | • Self-administered questionnaire completed by cases; telephone interviews conducted for 14% of controls who declined mailed questionnaire<br>• Data collected for smoking status (never and ever), duration, pack-years, age at initiation of smoking cigarettes/day, and timing with first pregnancy<br>• Subgroups evaluated and stratified by menopausal status | • No association between risk for breast cancer and active smoking based on ever smoked, duration (years) of smoking, cigarettes/day, pack-years, age at smoking initiation, or smoking relative to first birth<br>• Data missing for nearly 17% of cases and 25% of controls | **Ever:**<br>Never: 1.00<br>Ever: 1.00 (0.90–1.20)<br>**Ever: menopausal status**<br>Never: 1.00<br>PreM: 1.40 (0.70–2.50)<br>PostM: 1.00 (0.90–1.20)<br>**Duration (years):**<br>Never: 1.00<br>1–10: 0.70 (0.40–1.30)<br>11–30: 1.00 (0.80–1.30)<br>>30: 1.10 (0.90–1.20)<br>p trend = 0.58<br>**Cigarettes/day:**<br>Never: 1.00<br>1–10: 1.00 (0.90–1.30)<br>11–20: 1.10 (0.90–1.30)<br>>20: 0.80 (0.40–1.40)<br>p trend = 0.71<br>**Pack-years:**<br>Never: 1.00<br>1–10: 0.90 (0.70–1.20)<br>11–20: 1.00 (0.80–1.20)<br>21–30: 1.40 (1.10–1.70)<br>>30: 0.90 (0.70–1.20)<br>p trend = 0.77<br>**Age at smoking initiation:**<br>Never: 1.00<br><20: 1.20 (1.00–1.40)<br>20–29: 0.90 (0.70–1.10)<br>>30: 1.00 (0.70–1.30)<br>**Timing with first pregnancy:**<br>Never: 1.00<br>Before: 1.20 (0.90–1.40)<br>After: 1.00 (0.70–1.40) | Controlled for age, age at birth of first child, BMI, and alcohol use |

**Table 6.15*S* Continued**

| Study | Study population and design | Data collection/subgroup analyses | Findings for active cigarette smoking | Measures of active cigarette smoking RR (95% CI) | Confounders |
|---|---|---|---|---|---|
| Prescott et al. 2007 | • Population-based study designed to examine the effects of cigarette smoking on risk for breast cancer at an early age among United States-born non-Hispanic White, Hispanic White, and African American women<br>• 1998–2003<br>• 20–49 years of age<br>• 1,728 incident cases (invasive) recruited through the Los Angeles County Cancer Surveillance Program<br>• 441 controls recruited through neighborhood controls and matched on age (±5 years) and ethnicity<br>• Los Angeles, California | • In-person interviews<br>• Data collected for status (never, former, and current), duration, age at smoking initiation, lifetime average cigarettes/week, average cigarettes in past 5 years, 5-year period after menarche, smoking before 18 years of age, and before first full-term pregnancy | • No significant association between risk for breast cancer and any measure of smoking<br>• First-degree family history of breast or ovarian cancer did not modify the risk association between smoking and risk for breast cancer<br>• Results reported to be comparable when analysis was restricted to long-term smokers (≥20 years) and never smokers and when restricted to Stage I, II, III/IV of cancer (data not shown) | **Status:**<br>Never: 1.00<br>Ever: 0.99 (0.78–1.25)<br>Former: 1.04 (0.80–1.36)<br>Current: 0.89 (0.64–1.24)<br>**Duration (years):**<br>Never: 1.00<br>≤11: 0.94 (0.68–1.30)<br>>11–≤20: 0.93 (0.66–1.31)<br>>20: 1.12 (0.79–1.59)<br>p trend = 0.74<br>**Cigarettes/week:**<br>Never: 1.00<br>≤8: 0.87 (0.62–1.23)<br>>8–≤52: 1.06 (0.76–1.47)<br>>52: 1.03 (0.73–1.45)<br>p trend = 0.79<br>**Age at smoking initiation:**<br>Never: 1.00<br>>18: 0.94 (0.66–1.33)<br>>15–≤18: 1.20 (0.86–1.67)<br>≤15: 0.83 (0.59–1.16)<br>p trend = 0.68<br>**Timing with first pregnancy:**<br>Never: 1.00<br>Years Before First Birth:<br>≤10: 0.95 (0.71–1.27)<br>>10: 1.03 (0.75–1.43)<br>Years After First Birth:<br>0.97 (0.48–1.95) | Controlled for age, race, education, age at menarche, number of full-term pregnancies, age at first full-term pregnancy, alcohol use, and family history |

**Table 6.15*S* Continued**

| Study | Study population and design | Data collection/subgroup analyses | Findings for active cigarette smoking | Measures of active cigarette smoking RR (95% CI) | Confounders |
|---|---|---|---|---|---|
| Roddam et al. 2007 | • Designed to study the association between OC use and breast cancer risk in premenopausal women<br>• 1987–1990<br>• 36–45 years of age<br>• 639 cases (invasive) ascertained through regional and hospital registries<br>• 640 age-matched controls and randomly selected by general practitioners of the respective cases<br>• Thames, Oxford, and Yorkshire regions, United Kingdom | • In-person interviews<br>• Data collected for status, age at smoking initiation, duration, and cigarettes/day<br>• Analyses for duration, intensity (cigarettes/day), and age at smoking initiation based on continuous measures (results not shown)<br>• Data collected for exposure to secondhand smoke (see Table 6.23*S*) | • No association for active smoking and risk for breast cancer for current or former smoking, duration, or age at smoking initiation | **Status:**<br>Never: 1.00<br>Former: 1.15 (0.87–1.53)<br>Current: 1.04 (0.79–1.36)<br>**Status with NA/NP:**<br>NA/NP: 1.00<br>Passive: 0.89 (0.64–1.25)<br>Former, NP: 1.12 (0.72–1.73)<br>Former, P: 1.09 (0.75–1.56)<br>Current, NP: 1.19 (0.72–1.95)<br>Current, P: 0.93 (0.67–1.30)<br>**Duration (years):**<br>Per 5 years: 1.00 (0.91–1.11)<br>**Cigarettes/day:**<br>Never: 1.00<br>5/day: 1.00 (0.89–1.12)<br>**Age at smoking initiation:**<br>Per 5 years: 0.97 (0.79–1.19) | Controlled for age, geographic region, socioeconomic status, alcohol use, BMI, parity, age at first live birth, OC use, family history, age at menarche, menopausal status, and active/passive exposure |

**Table 6.15*S* Continued**

| Study | Study population and design | Data collection/subgroup analyses | Findings for active cigarette smoking | Measures of active cigarette smoking RR (95% CI) | Confounders |
|---|---|---|---|---|---|
| Rollison et al. 2008 | • Population-based study designed to evaluate smoking and breast cancer risk<br>• 2000–2002<br>• 40–79 years of age<br>• 287 primary incident cases (invasive) ascertained through the Delaware Cancer Registry<br>• 311 controls selected from motor vehicle driver's license records (<65 years) and from Health Care Financing Administration records for Delaware (≥65 years)<br>• Delaware | • Telephone interviews<br>• Data collected for ever, age at smoking initiation, duration, number of years smoked before 18 years of age and before first live birth, pack-years, cigarettes/day, types of tobacco products used, and inhalation pattern<br>• Data collected for exposure to secondhand smoke (see Table 6.23*S*)<br>• Subgroups evaluated and stratified by menopausal status | • No significant association between risk for breast cancer and any smoking measure<br>• No significant association between risk and any smoking measure when a no active/no passive referent group was used, regardless of definition of passive exposure no residential smoking before the age of 18; ≤10 years of residential and occupational smoking; and no residential and occupational smoking | **Ever:**<br>Never: 1.00<br>Ever: 1.43 (1.03–1.99)<br>PreM: 1.53 (0.60–3.95)<br>PostM: 1.36 (0.95–1.94)<br>**Ever with NA/NP:**<br>NA/NP: 1.00<br>Ever, no residential: 1.23 (0.76–1.98)<br>**Duration (years):**<br>Never: 1.00<br><10: 1.36 (0.72–2.55)<br>10–19: 1.13 (0.64–2.01)<br>20–29: 1.80 (1.02–3.20)<br>30–39: 1.31 (0.76–2.25)<br>40–49: 1.50 (0.79–2.82)<br>50–62: 1.21 (0.52–2.84)<br>**Cigarettes/day:**<br>Never: 1.00<br><10: 1.60 (1.01–2.53)<br>10–19: 1.53 (0.99–2.35)<br>20–29: 1.12 (0.61–2.04)<br>30–68: 0.84 (0.34–2.08)<br>**Pack-years:**<br>Never: 1.00<br><5: 1.45 (0.85–2.45)<br>5–9: 1.65 (0.81–3.35)<br>10–19: 1.83 (1.04–3.23)<br>20–29: 1.24 (0.69–2.24)<br>30–39: 1.06 (0.44–2.56)<br>40–49: 1.92 (0.81–4.55)<br>50–102: 0.75 (0.34–1.65)<br>**Timing with first pregnancy: before (years)**<br>Never: 1.00<br><5: 1.25 (0.73–2.13)<br>5–9: 1.37 (0.87–2.16)<br>10–14: 0.69 (0.33–1.45)<br>15–39: 1.99 (0.76–5.18) | Controlled for age, education, and menopausal status in final models; further adjustment for reproductive factors, alcohol use, BMI, and FH did not change estimates by more than 10% |

**Table 6.15*S* Continued**

| Study | Study population and design | Data collection/subgroup analyses | Findings for active cigarette smoking | Measures of active cigarette smoking RR (95% CI) | Confounders |
|---|---|---|---|---|---|
| Slattery et al. 2008 | • 4-Corners Breast Cancer Study<br>• Population-based study designed to evaluate risk factors for breast cancer among Hispanic, American Indian, and non-Hispanic White women in southwestern United States<br>• 1999–2004<br>• 25–79 years of age<br>• 2,325 incident cases (in situ, invasive): ascertained through cancer registries<br>• 2,525 controls frequency-matched on ethnicity and 5-year age groups; women <65 years of age selected from commercial mailing lists (in Arizona and Colorado) or from driver license lists; women ≥65 years of age selected from Centers for Medicare & Medicaid Services list<br>• Statewide for Utah, New Mexico, and Colorado and 7 counties in Arizona | • In-person interview<br>• Data collected for smoking status (never, former, and current), age at initiation, duration, usual amount smoked, and smoking before or after first pregnancy<br>• Genotype assays for 5 *IL6* markers and 1 *ESR1* marker<br>• Data collected for exposure to secondhand smoke (see Table 6.23*S*)<br>• Subgroups evaluated and stratified by menopausal status ethnicity, and genotype | • Risk for breast cancer significantly associated with ever smoked, pack-years, and smoking before first full-term birth in premenopausal non-Hispanic White women only. | **Status: premenopausal, non-Hispanic White**<br>Never: 1.00<br>Ever: 1.30 (1.00–1.70)<br>Former: 1.40 (1.00–1.80)<br>Current: 1.30 (0.90–1.90)<br>p trend = 0.09<br>**Hispanic**<br>Never: 1.00<br>Ever: 1.10 (0.70–1.50)<br>Former: 1.10 (0.80–1.70)<br>Current: 0.90 (0.50–1.60)<br>p trend = 0.98<br>**Status: postmenopausal, non-Hispanic White**<br>Never: 1.00<br>Ever: 1.00 (0.90–1.20)<br>Former: 1.10 (0.90–1.30)<br>Current: 1.00 (0.70–1.30)<br>p trend = 0.96<br>**Hispanic**<br>Never: 1.00<br>Ever: 1.00 (0.70–1.30)<br>Former: 0.90 (0.70–1.30)<br>Current: 1.00 (0.70–1.50)<br>p trend = 0.84<br>**Pack-years: premenopausal, non-Hispanic White**<br>Never: 1.00<br>1–15: 1.10 (0.80–1.60)<br>>15: 1.60 (1.10–2.40)<br>p trend = 0.03<br>**Hispanic**<br>Never: 1.00<br>1–15: 1.00 (0.70–1.60)<br>>15: 0.90 (0.50–1.70)<br>p trend = 0.88 | Controlled for age, center, BMI, aspirin use, NSAIDs, parity, alcohol use, physical activity, and recent (±2 years) estrogen exposure for postmenopausal women |

**Table 6.15*S* Continued**

| Study | Study population and design | Data collection/subgroup analyses | Findings for active cigarette smoking | Measures of active cigarette smoking RR (95% CI) | Confounders |
|---|---|---|---|---|---|
| Slattery et al. 2008 (continued) | | | | **Pack-Years: postmenopausal, non-Hispanic White**<br>Never: 1.00<br>1–15: 1.20 (0.90–1.50)<br>>15: 1.00 (0.80–1.20)<br>p trend = 0.90<br>**Hispanic**<br>Never: 1.00<br>1–15: 0.70 (0.50–1.00)<br>>15: 1.20 (0.80–1.70)<br>p trend = 0.96<br>**Age at smoking initiation: premenopausal, non-Hispanic White**<br>Never: 1.00<br>≥20: 1.40 (0.90–2.30)<br>17–19: 1.20 (0.80–1.80)<br>≤16: 1.30 (0.90–1.90)<br>p trend = 0.08<br>**Hispanic**<br>Never: 1.00<br>≥20: 1.10 (0.60–1.90)<br>17–19: 1.10 (0.60–1.90)<br>≤16: 1.00 (0.60–1.70)<br>p trend = 0.84<br>**Age at smoking initiation: postmenopausal, non-Hispanic White**<br>Never: 1.00<br>≥20: 1.20 (0.90–1.60)<br>17–19: 1.00 (0.80–1.20)<br>≤16: 0.90 (0.70–1.20)<br>p trend = 0.51<br>**Age at smoking initiation: postmenopausal, hispanic**<br>Never: 1.00<br>≥20: 1.00 (0.70–1.40)<br>17–19: 1.00 (0.70–1.60)<br>≤16: 0.90 (0.60–1.30)<br>p trend = 0.65 | |

**Table 6.15*S* Continued**

| Study | Study population and design | Data collection/subgroup analyses | Findings for active cigarette smoking | Measures of active cigarette smoking RR (95% CI) | Confounders |
|---|---|---|---|---|---|
| Slattery et al. 2008 (continued) | | | | **Timing with first pregnancy: premenopausal, non-Hispanic White**<br>**Before**<br>Never: 1.00<br>No: 1.20 (0.60–2.40)<br>Yes: 1.40 (1.00–1.90)<br>p trend = 0.03<br>**Timing with first pregnancy: premenopausal, hispanic**<br>**Before**<br>Never: 1.00<br>No: 1.00 (0.50–2.10)<br>Yes: 1.10 (0.80–1.70)<br>p trend = 0.56<br>**Timing with first pregnancy: postmenopausal, non-Hispanic White**<br>**Before**<br>Never: 1.00<br>No: 1.00 (0.70–1.40)<br>Yes: 1.00 (0.80–1.30)<br>p trend = 0.83<br>**Timing with first pregnancy: postmenopausal, hispanic**<br>**Before**<br>Never: 1.00<br>No: 1.20 (0.80–1.80)<br>Yes: 0.90 (0.70–1.20)<br>p trend = 0.66 | |

**Table 6.15*S* Continued**

| Study | Study population and design | Data collection/subgroup analyses | Findings for active cigarette smoking | Measures of active cigarette smoking RR (95% CI) | Confounders |
|---|---|---|---|---|---|
| Ahern et al. 2009[a] | • Population-based study designed to evaluate the association between breast cancer risk and lifestyle factors<br>• 1989–1991<br>• 28–75 years of age<br>• 557 incident cases (invasive) ascertained through the Massachusetts Cancer Registry<br>• 432 controls selected randomly from the driver's license bureau (<65 years) and from Massachusetts Medicare rosters (≥65 years)<br>• Massachusetts | • Telephone interview<br>• Data collected for smoking status (never, former, and current), age at smoking initiation, age at smoking cessation, and pack-years<br>• Age at smoking initiation and cessation reported only as continuous measures<br>• Data collected for exposure to secondhand smoke (see Table 6.23*S*)<br>• Subgroups evaluated and stratified by menopausal status for pack-years | • No association between risk for breast cancer and pack-years, regardless of whether a no active or a no active/no passive referent group was used<br>• No association in analyses stratified by menopausal status (data not reported) | **Pack-years:**<br>Never: 1.00<br>1–23: 1.20 (0.90–1.70)<br>≥24: 0.90 (0.70–1.30)<br>NA/NP: 1.00<br>1–23: 0.70 (0.40–1.50)<br>≥24: 0.60 (0.30–1.20)<br>**Pack-years: premenopausal**<br>Never: 1.00<br>1–23: 1.50 (0.90–2.40)<br>≥24: 0.80 (0.40–1.60)<br>**Pack-years: postmenopausal**<br>Never: 1.00<br>1–23: 1.10 (0.70–1.60)<br>≥24: 1.00 (0.60–1.40) | Controlled for age, BMI, menopausal status, parity, alcohol use, and family history<br>Active smoking additionally adjusted for exposure to secondhand smoke |

**Table 6.15*S* Continued**

| Study | Study population and design | Data collection/subgroup analyses | Findings for active cigarette smoking | Measures of active cigarette smoking RR (95% CI) | Confounders |
|---|---|---|---|---|---|
| Young et al. 2009 | • Secondary analysis to evaluate the association between smoking and breast cancer risk using data from 2 population-based studies with similar target populations and data collection methods.<br>• OWHS<br>• 1996–1998<br>• OWDHS<br>• 2002–2003<br>• 25–75 years of age<br>• 6,235 incident cases (invasive) ascertained through Ontario Cancer Registry (50% random sample of cases from OWHS, and all cases in 11-month window from OWDHS)<br>• 6,533 controls frequency-matched by 5-year age groups and selected randomly (age-stratified) from the Ontario Ministry of Finance rolls (for OWHS) and from a random-digit dialing list (for OWDHS)<br>• Canada | • Self-administered, mailed questionnaire<br>• Data collected for a history of smoking 100 or more cigarettes, age at smoking initiation and in relation to timing of first birth<br>• Data collected for exposure to secondhand smoke (see Table 6.23*S*)<br>• Subgroups evaluated and stratified by age at menarche and age at first live birth | • No association between risk for breast cancer and only active smoking<br>• Increased risk detected for active smoking combined with exposure to secondhand smoke<br>• Trend for increased risk associated with older age at smoking initiation<br>• Increased risk associated with smoking >5 years before and after first birth<br>• Risk patterns similar when analyses stratified by age at menarche and by age at first live birth | **Ever with NA/NP:**<br>NA/NP: 1.00<br>Active: 1.10 (0.98–1.23)<br>Active and Passive: 1.13 (1.01–1.25)<br>**Age at smoking initiation with NA/NP:**<br>NA/NP: 1.00<br><12: 0.88 (0.59–1.31)<br>12–15: 1.02 (0.90–1.16)<br>16–20: 1.12 (1.01–1.24)<br>21–25: 1.13 (0.96–1.33)<br>≥26: 1.26 (1.03–1.55)<br>**Timing with first pregnancy with NA/NP: before (years)**<br>NA/NP: 1.00<br>>5: 1.16 (1.04–1.31)<br>≤5: 0.96 (0.84–1.09)<br>**Timing with first pregnancy with NA/NP: after**<br>NA/NP: 1.00<br>After 1.24 (1.02–1.52) | Controlled for age at menarche, age at first live birth, parity, menopausal status, family history of benign breast disease, BMI, OC use, HRT, alcohol use, and household income |

**Table 6.15*S* Continued**

| Study | Study population and design | Data collection/subgroup analyses | Findings for active cigarette smoking | Measures of active cigarette smoking RR (95% CI) | Confounders |
|---|---|---|---|---|---|
| Andonova et al. 2010[a] | • GENICA (Gene Environment Interaction and Breast Cancer in Germany) study<br>• Population-based study designed to evaluate the risk of breast cancer among lifestyle, tumor, and genetic factors (polymorphisms in *GST*)<br>• 2000–2004<br>• <80 years of age<br>• 1,143 incident cancer cases (in situ, invasive) ascertained through linkage with 14 surrounding hospitals in the study region; analyses based on 1,021 (89%)<br>• 1,155 controls selected randomly through population registries in 31 communities and frequency-matched to cases by year of birth (5-year groups); analyses based on 1,015 (88%)<br>• Greater Bonn region, Germany | • In-person interviews<br>• Data collected for status (never, former, current)<br>• Genotype assays for 9 *GST* polymorphisms | • No significant association with smoking status and risk of breast cancer<br>• No significant association with smoking status and *GST* polymorphisms (data not shown)<br>• Results evaluated for main effects of genotypes by smoking status but not for modification of effects of smoking by genotypes | **Status:**<br>Never: 1.00<br>Former: 0.95 (0.75–1.19)<br>Current: 0.84 (0.66–1.06) | Controlled for menopausal status, family history of breast cancer, OC use, HRT, and BMI |

**Table 6.15*S* Continued**

| Study | Study population and design | Data collection/subgroup analyses | Findings for active cigarette smoking | Measures of active cigarette smoking RR (95% CI) | Confounders |
|---|---|---|---|---|---|
| Brown et al. 2010 | • Population-based study designed to evaluate the effect of alcohol consumption and cigarette smoking on risk for breast cancer among Asian-Americans (Chinese, Japanese, Filipino)<br>• 1983–1987<br>• 20–55 years of age<br>• 597 incident cases (in situ, invasive) ascertained through linkage with SEER<br>• 966 controls<br>• selected by random-digit dialing in San Francisco-Oakland and Los Angeles; and the Health Surveillance Program of the Hawaii State Department of Health and frequency-matched to cases (2:1) by study area, age (5-year groups), and ethnicity<br>• San Francisco-Oakland, Los Angeles, California; Oahu, Hawaii | • In-person interview<br>• Data collected for status (never, former, and current), duration, cigarettes/day, age at initiation and cessation, and years since cessation<br>• Current smokers were those who reported smoking regularly for ≥6 months; former smokers were those who had not smoked for ≥2 years | • No association between risk for breast cancer and ever or current status, duration, or cigarettes/day<br>• Risk for breast cancer significantly increased for former smoking and age at initiation <16 years<br>• No difference when assessing migration history and risk of breast cancer when including cigarettes/day as a confounder | **Status:**<br>Never: 1.0<br>Ever: 1.2 (0.9-1.6)<br>Former: 1.6 (1.1–2.2)<br>Current: 0.9 (0.6–1.3)<br>**Duration (years):**<br>Never: 1.0<br><10: 1.3 (0.8–2.1)<br>10–19: 1.1 (0.7–1.7)<br>20–29: 1.4 (0.9–2.0)<br>>29: 0.9 (0.5–1.6)<br>**Cigarettes/day:**<br>Never: 1.0<br><10: 1.2 (0.8–1.7)<br>10–19: 1.3 (0.9–2.1)<br>20: 1.2 (0.8–1.9)<br>≥21: 0.9 (0.5–1.9)<br>**Age at smoking initiation:**<br>Never: 1.00<br><16: 2.92 (1.1–7.9)<br>16–18: 1.18 (0.7–1.9)<br>19–21: 1.03 (0.7–1.5)<br>≥22: 1.20 (0.8–1.8) | Controlled for age, study area, ethnicity, age at menarche, age at first live birth, number of live births, menopausal status, age at menopause, family history, and history of benign breast disease |

**Table 6.15*S* Continued**

| Study | Study population and design | Data collection/subgroup analyses | Findings for active cigarette smoking | Measures of active cigarette smoking RR (95% CI) | Confounders |
|---|---|---|---|---|---|
| Gibson et al. 2010 | • Nested case-control study within a clinical cohort trial to evaluate use of clinical breast exams as an alternative to mammography.<br>• 1995–2001<br>• 35–64 years of age<br>• 123 incident cancer cases (invasive) ascertained through cancer society and cancer registries<br>• 978 controls selected and matched to cases by age, residence, date of clinical breast exam in an 8:1 ratio<br>• Manila, Philippines | • In person interview<br>• Data on status (never, ever) | • No association among ever smokers and risk of breast cancer | **Status:**<br>Never: 1.00<br>Ever: 1.3 (0.6–2.9) | Controlled for age, municipality, parity, age at first full-term pregnancy, and education |
| Kaushal et al. 2010 | • Population-based study to evaluate association of genetic polymorphisms with breast cancer risk<br>• 2005–2008<br>• Mean age: 45–46 years<br>• 117 incident cancer cases (invasive) ascertained through hospital referral and cancer registry<br>• 174 controls selected from individuals accompanying the hospital patient; matched to cases by gender and age (±5 years)<br>• Northeast India | • In-person interviews<br>• Data collected for current smoking status<br>• Genotype assays for *GSTT1*, *GSTM1*, *GSTP1*, *TP53* and *CYP17* | • No association of cigarette smoking with risk of breast cancer | **Ever:**<br>No: 1.00<br>Yes: 1.15 (0.62–2.13) | None listed |

**Table 6.15*S* Continued**

| Study | Study population and design | Data collection/subgroup analyses | Findings for active cigarette smoking | Measures of active cigarette smoking RR (95% CI) | Confounders |
|---|---|---|---|---|---|
| Rabstein et al. 2010[a] | • GENICA (Gene Environment Interaction and Breast Cancer in Germany) study<br>• Population-based study designed to evaluate the risk of breast cancer among lifestyle, tumor, and *NAT2* polymorphisms<br>• 2000-2004<br>• <80 years of age<br>• 1,143 incident cancer cases (in situ, invasive) ascertained through linkage with 14 surrounding hospitals in the study region<br>• 1,155 controls selected randomly through population registries in 31 communities and frequency-matched to cases by year of birth (5-year groups)<br>• Greater Bonn region, Germany | • In person interviews<br>• Data collected on status (never, former, current)<br>• Genotype assays for *NAT2*<br>• Subgroups evaluated and stratified by *NAT2* and hormone-receptor status | • No association with smoking status<br>• No association with ER status or NAT2 genotype; interaction term was not significant | **Status:**<br>Never: 1.00<br>Former: 0.82 (0.65–1.03)<br>Current: 0.99 (0.71–1.11) | Controlled for family history, HRT, mammogram frequency, physical activity, and lifetime breastfeeding |
| Cerne et al. 2011 | • Institute of Oncology<br>• Population-based study designed to evaluate risk factors for breast cancer<br>• 2006–2008<br>• 50–69 of age<br>• 825 incident cancer cases (in situ, invasive) ascertained through the Institute of Oncology<br>• 732 controls selected from the Department of Obstetrics and Gynecology, University Medical Centre<br>• Ljubljana, Slovenia | • Self-administered questionnaire<br>• Data collected on current smoking status and cigarettes/day | • Significant increase in risk for breast cancer among current smokers who smoke ≥10 cigarettes/day | **Cigarettes/day: current**<br>Nonsmoker: 1.00<br><10: 1.56 (0.88–2.77)<br>≥10: 1.70 (1.20–2.43) | Controlled for age and education |

**Table 6.15*S* Continued**

| Study | Study population and design | Data collection/subgroup analyses | Findings for active cigarette smoking | Measures of active cigarette smoking RR (95% CI) | Confounders |
|---|---|---|---|---|---|
| DeRoo et al. 2011a | • Case-control study designed to evaluate the association between smoking during first pregnancy and breast cancer risk.<br>• 1985–2000<br>• ≤65 years of age<br>• 1,099 incident cases (in-situ, invasive) ascertained through the population-based cancer registries<br>• 10,922 controls selected by linkage with Department of Licensing data; up to 10 controls were matched to cases by year, age at first birth, race/ethnicity and birth outcome<br>• Washington state | • Data was collected by linkage to state birth and fetal death records and vital records for maternal characteristics<br>• Any smoking reported during first pregnancy was defined as exposure | • No association for smoking during first pregnancy and risk of breast cancer | **Status: during first pregnancy**<br>No: 1.00<br>Yes: 0.8 (0.7–0.9)<br>**Status during first pregnancy: residents for at least 5 years**<br>No: 1.00<br>Yes: 1.0 (0.8–1.1) | Controlled for age at first birth, year of delivery, race/ethnicity, birth outcome, and imputed and known maternal prenatal alcohol use |

*Note:* Study-specific results are not intended to be a complete reporting of all findings. When available, results for ever, status, duration, cigarettes/day, pack-years, age at initiation, and timing with first pregnancy (smoking before or during first pregnancy) are reported. Unless otherwise specified, the definition of the reference group is based on a no active-only exposure, which includes individuals with secondhand smoke exposure. When available, results for ever smoking using a no active/no passive reference group are reported; however, similar results for the other measures are not reported in the table. Data from case-control studies for exposure to secondhand smoke are summarized in Table 6.25*S*. All results reported by the study may not appear in the summary table. **BMI** = body mass index; **cig/day =** cigarettes smoked per day; **CI** = confidence interval; **CVD** = cardiovascular disease; **ER** = estrogen receptor; **HRT** = hormone replacement therapy; **NAT2** = Nacetyltransferase 2; **NA/NP** = no active/no passive; **NSAIDs** = nonsteroidal anti-inflammatory drugs; **OC** = Oral contraceptive; **OR** = odds ratio; **OWDHS** = Ontario Women's Diet and Health Study; **OWHS** = Ontario Women's Health Study; **P** = passive; **pack-years** = the number of years of smoking multiplied by the number of packs of cigarettes smoked per day; **PostM** = postmenopausal; **PreM** = premenopausal; **PR** = progesterone receptor; **RR** = relative risk; **SEER** = Surveillance, Epidemiology, and End Results; **USDHHS** = United States Department of Health and Human Services.

[a]Report that overlaps with another from the same study population shown in this table and reported in Table 6.16*S*A.

**Table 6.16*S*** **Evaluation of reports on exposure to active cigarette smoking for meta-analyses, based on cohort studies before 2012 and case-control studies published between 2000 and 2011 for meta-analyses, by location, study design, size of analytic sample, type of referent group, meta-analysis categories, and design or analysis issues (n = 65)**

| | | | Type of referent group | | Meta-analysis categories | | | | | | | Design and analysis issues | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study** | **Design/population** | **Analytic sample size** | **No active-only** | **No active/no passive** | **Ever** | **Current** | **Former** | **Duration** | **Cigarettes/day** | **Pack-years** | **Age at initiation** | **Before/during first pregnancy** | **Small sample** | **Mixed referent or inadequate adjustment or proxy** | **Cut-point/outlier** |
| **A. Overlapping reports, included in meta-analyses only if most recent or most complete (n = 26)** | | | | | | | | | | | | | | | |
| Hiatt and Bawol et al. 1984[a] | • KPMCP<br>• 1964–1972<br>• Cohort<br>• United States | 1,169 of 88,477 | 1 | — | 1 | — | — | — | — | — | — | — | — | — | — |
| Hiatt and Fireman 1986[b] | — | 1,363 of 84,172 | 1 | — | 1 | 1 | 1 | — | 1 | — | — | — | — | — | — |
| Willett et al. 1987[a] | • NHS-I<br>• Cohort<br>• United States | 1,224 of 5,599 | 1 | — | 1 | — | — | — | — | — | — | — | — | — | — |
| London et al. 1989 | — | 1,788 of 117,557 | 1 | — | 1 | 1 | 1 | — | 1 | — | — | — | — | — | — |
| Hunter et al. 1997 | • Nested case-control | 466/466 | 1 | — | 1 | 1 | 1 | — | 1 | 1 | — | 1 | — | — | — |
| Egan et al. 2002[b] | — | 3,140 of 78,206 | 1 | 1 | 1 | 1 | 1 | 1 | — | — | 1 | 1 | — | — | — |
| Xue et al. 2011[b,c] | — | 8,772 of 111,140 | 1 | — | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | — | — | — |

**Table 6.16*S* Continued**

| Study | Design/population | Analytic sample size | Type of referent group | | Meta-analysis categories | | | | | | | Design and analysis issues | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | No active-only | No active/no passive | Ever | Current | Former | Duration | Cigarettes/day | Pack-years | Age at initiation | Before/during first pregnancy | Small sample | Mixed referent or inadequate adjustment or proxy | Cut-point/outlier |
| Gapstur et al. 1992[a] | • IWHS<br>• Cohort<br>• United States | 679 of 2,725 | 1 | — | 1 | — | — | — | — | — | — | — | — | — | — |
| Olson et al. 2005[b] | — | 2,017 of 37,105 | 1 | — | 1 | 1 | 1 | 1 | — | 1 | 1 | 1 | — | — | — |
| Friedenreich et al. 1993[a] | • NBSS<br>• Cohort<br>• Canada | 181 of 662 | 1 | — | 1 | — | — | — | — | — | — | — | — | — | — |
| Terry et al. 2002 | — | 2,552 of 56,837 | 1 | — | 1 | 1 | 1 | 1 | 1 | 1 | 1 | — | — | — | — |
| Cui et al. 2006[b] | — | 4,434 of 49,613 | 1 | — | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | — | — | — |
| Kabat et al. 2011 | • WHI<br>• Cohort<br>• United States | 300 (TNBC) & 2,479 (ER+) of 148,030 | 1 | — | 1 | 1 | 1 | 1 | 1 | 1 | 1 | — | — | — | — |
| Luo et al. 2011b[b] | — | 3,520 of 79,990 | EV<br>ST<br>D<br>CD<br>PY<br>AI<br>FB | EV<br>ST<br>D<br>CD<br>PY<br>AI<br>FB | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | — | — | — |
| Manjer et al. 2000b[b] | • Cohort<br>• Malmo, Sweden | 414 of 10,849 | 1 | — | 1 | 1 | 1 | — | 1 | — | — | — | — | — | — |
| Manjer et al. 2001 | — | 297 of 10,849 | 1 | — | 1 | 1 | 1 | — | 1 | — | — | — | — | — | — |

**Table 6.16*S* Continued**

| Study | Design/population | Analytic sample size | Type of referent group | | Meta-analysis categories | | | | | | | Design and analysis issues | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | No active-only | No active/no passive | Ever | Current | Former | Duration | Cigarettes/day | Pack-years | Age at initiation | Before/during first pregnancy | Small sample | Mixed referent or inadequate adjustment or proxy | Cut-point/outlier |
| Marcus et al. 2000 | • Carolina BCS<br>• Case-control<br>• United States | 864/790 | 1 | — | 1 | 1 | 1 | 1 | 1 | — | 1 | — | — | — | — |
| Mechanic et al. 2006[b] | — | 2,308/2,022 | — | 1 | 1 | 1 | 1 | 1 | 1 | — | 1 | — | — | — | — |
| Egan et al. 2003[b] | • Case-control | 791/797 | 1 | — | 1 | — | — | — | — | 1 | 1 | — | — | — | — |
| Ahern et al. 2009[b] | — | 557/432 | EV PY | EV PY | 1 | — | — | — | — | 1 | — | — | — | — | — |
| Gammon et al. 2004a[b] | • Case-control | 1,356/1,383 | — | 1 | 1 | 1 | 1 | — | 1 | 1 | 1 | 1 | — | — | — |
| Mordukhovich et al. 2010 | — | 128 p53+, 731 p53$^-$ | — | 1 | 1 | 1 | 1 | — | — | — | — | — | — | — | — |
| Metsola et al. 2005 | • KBCS<br>• Case-control<br>• Finland | 475/481 | — | 1 | 1 | — | — | — | — | 1 | — | — | — | 1 | 1 |
| Sillanpaa et al. 2005a[b] | — | 479/482 | — | 1 | 1 | 1 | 1 | — | — | 1 | — | — | — | — | 1 |
| Andonova et al. 2010[b] | • GENICA<br>• Case-control<br>• Germany | 1,020/1,015 | 1 | 1 | 1 | 1 | 1 | — | — | — | — | — | — | — | — |
| Rabstein et al. 2010 | — | 1,019/1,047 | 1 | 1 | 1 | 1 | 1 | — | — | — | — | — | — | 1 | — |

**Table 6.16*S* Continued**

| Study | Design/population | Analytic sample size | Type of referent group | | Meta-analysis categories | | | | | | | Design and analysis issues | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | No active-only | No active/no passive | Ever | Current | Former | Duration | Cigarettes/day | Pack-years | Age at initiation | Before/during first pregnancy | Small sample | Mixed referent or inadequate adjustment or proxy | Cut-point/outlier |
| **B. Nonoverlapping reports (n = 39)** | | | | | | | | | | | | | | | |
| Hiatt et al. 1988 | • KPMCP<br>• 1978–1984<br>• Cohort<br>• United States | 303 of 68,674 | 1 | — | 1 | 1 | 1 | — | 1 | — | — | — | — | — | — |
| Schatzkin et al. 1989 | • Framingham Heart Study<br>• Cohort<br>• Massachusetts | 143 of 2,636 | 1 | — | 1 | 1 | — | — | — | — | — | — | 1 | 1 | — |
| Vatten and Kvinnsland 1990 | • Cohort<br>• Norway (3 counties) | 242 of 24,329 | 1 | — | 1 | 1 | — | — | — | — | — | — | — | 1 | — |
| van den Brandt et al. 1995[a] | • Netherlands Cohort Study<br>• Cohort<br>• Netherlands | 119 of 504 | 1 | — | 1 | — | — | — | — | — | — | — | — | — | — |
| Engeland et al. 1996 | • The Migrant Study<br>• Cohort<br>• Norway site | 603 of 14,269 | 1 | — | 1 | 1 | 1 | — | — | — | — | — | — | 1 | — |
| Nordlund et al. 1997 | • Cohort<br>• Linkopings, Sweden | 996 of 26,032 | 1 | — | 1 | 1 | 1 | — | 1 | — | 1 | — | — | 1 | — |
| Million Women Study Collaborative Group 1999[a] | • MWS<br>• Cohort<br>• United Kingdom | 324 of 1,291 | 1 | — | 1 | — | — | — | — | — | — | — | — | — | — |
| Innes and Byers 2001 | • Case-control<br>• New York | 310/732 | 1 | — | — | — | — | — | — | — | — | 1 | — | — | — |

**Table 6.16*S* Continued**

| Study | Design/population | Analytic sample size | Type of referent group | | Meta-analysis categories | | | | | | | Design and analysis issues | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | No active-only | No active/no passive | Ever | Current | Former | Duration | Cigarettes/day | Pack-years | Age at initiation | Before/during first pregnancy | Small sample | Mixed referent or inadequate adjustment or proxy | Cut-point/outlier |
| Delfino et al. 2000 | • Case-control<br>• California | 109/270 | — | 1 | 1 | 1 | 1 | 1 | 1 | — | — | — | 1 | — | — |
| Johnson et al. 2000 | • NECSS<br>• Case-control<br>• Canada | 2,304/2,429 | EV<br>ST | EV<br>ST<br>D<br>CD<br>PY<br>AI | 1 | 1 | 1 | 1 | 1 | 1 | 1 | — | — | — | — |
| Morabia et al. 2000 | • Case-control<br>• Geneva, Switzerland | 160/162 | — | 1 | 1 | — | — | — | — | — | — | — | 1 | 1 | — |
| Band et al. 2002 | • Case-control<br>• British Columbia, Canada | 1,018/1,025 | 1 | — | 1 | — | — | 1 | 1 | 1 | — | 1 | — | — | — |
| Kropp and Chang-Claude 2002 | • Case-control<br>• Mannheim, Germany | 468/1,087 | — | 1 | 1 | 1 | 1 | 1 | — | 1 | 1 | 1 | — | — | |
| Lash and Aschengrau 2002 | • Case-control<br>• Massachusetts | 441/419 | — | 1 | 1 | — | — | 1 | 1 | — | 1 | 1 | — | 1 | — |
| Zheng et al. 2002b | • Case-control<br>• Connecticut | 338/345 | 1 | — | 1 | 1 | 1 | 1 | 1 | 1 | 1 | — | — | — | |
| Fink and Lash 2003 | • Case-control<br>• Massachusetts | 1,878/5,632 | 1 | — | — | — | — | — | — | — | — | 1 | — | — | — |
| van der Hel et al. 2003 | • MPCDRF<br>• Case-control<br>• Netherlands | 229/263 | 1 | — | 1 | — | — | 1 | 1 | — | — | — | — | — | |

**Table 6.16*S* Continued**

| Study | Design/population | Analytic sample size | Type of referent group | | Meta-analysis categories | | | | | | | Design and analysis issues | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | No active-only | No active/no passive | Ever | Current | Former | Duration | Cigarettes/day | Pack-years | Age at initiation | Before/during first pregnancy | Small sample | Mixed referent or inadequate adjustment or proxy | Cut-point/outlier |
| Alberg et al. 2004[d] | • CLUE-II/U.S.<br>• Case-control<br>• United States | 115/115 | EV<br>ST | EV<br>ST | 1 | 1 | 1 | — | — | 1 | — | — | 1 | 1 | — |
| Al-Delaimy et al. 2004 | • NHS-II<br>• Cohort<br>• United States | 1,007 of 112,844 | 1 | — | 1 | 1 | 1 | 1 | 1 | — | 1 | 1 | — | — | |
| Reynolds et al. 2004b | • CTS/U.S.<br>• Cohort<br>• United States | 2,005 of 116,544 | EV<br>ST<br>CD<br>AI<br>FB | EV<br>ST | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | — | — | |
| Lawlor et al. 2004 | • Cohort<br>• Bristol, United Kingdom | 139 of 3,407 | 1 | — | — | — | — | — | — | — | — | 1 | — | — | — |
| Gram et al. 2005 | • N-SWLHCS<br>• Cohort<br>• Norway, Sweden | 1,130 of 102,098 | EV | EV<br>ST<br>D<br>CD<br>PY<br>AI<br>FB | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | — | — | — |
| Hanoaka et al. 2005 | • JPHC<br>• Cohort<br>• Japan | 180 of 21,805 | EV<br>ST | EV<br>ST | 1 | 1 | 1 | — | — | — | — | — | 1 | — | — |

**Table 6.16*S* Continued**

| Study | Design/population | Analytic sample size | Type of referent group | | Meta-analysis categories | | | | | | | Design and analysis issues | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | No active-only | No active/no passive | Ever | Current | Former | Duration | Cigarettes/day | Pack-years | Age at initiation | Before/during first pregnancy | Small sample | Mixed referent or inadequate adjustment or proxy | Cut-point/outlier |
| Li et al. 2005 | • Case-control<br>• Washington | 939/963 | 1 | — | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | — | — | 1 |
| Lissowska et al. 2006 | • Case-control<br>• Warsaw and Lodz, Poland | 2,374/2,498 | EV<br>ST<br>D<br>CD<br>AI<br>FB | EV | 1 | 1 | 1 | 1 | 1 | — | 1 | 1 | — | — | 1 |
| Ha et al. 2007 | • RTS<br>• Cohort<br>• United States | 906 of 56,042 | 1 | — | 1 | 1 | 1 | — | — | — | 1 | 1 | — | — | 1 |
| Kruk 2007 | • Case-control<br>• West Pomerania, Poland | 857/1,084 | 1 | — | 1 | 1 | — | — | 1 | — | — | — | — | — | 1 |
| Magnusson et al. 2007 | • Case control<br>• Sweden | 2,784/2,583 | 1 | — | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | — | — | 1 |
| Prescott et al. 2007 | • Case-control<br>• California | 1,728/441 | 1 | — | 1 | 1 | 1 | 1 | — | — | 1 | 1 | — | — | — |
| Roddam et al. 2007[c] | • Case-control<br>• Thames, Oxford, and Yorkshire, United Kingdom | 639/640 | EV<br>ST<br>D<br>CD<br>AI | EV<br>ST | 1 | 1 | 1 | 1 | 1 | — | 1 | — | — | — | 1 |
| Lin et al. 2008 | • JCCS<br>• Cohort<br>• Japan | 208 of 34,401 | 1 | — | 1 | 1 | 1 | — | — | — | — | — | 1 | — | — |

**Table 6.16*S* Continued**

| Study | Design/population | Analytic sample size | Type of referent group | | Meta-analysis categories | | | | | | | Design and analysis issues | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | No active-only | No active/no passive | Ever | Current | Former | Duration | Cigarettes/day | Pack-years | Age at initiation | Before/during first pregnancy | Small sample | Mixed referent or inadequate adjustment or proxy | Cut-point/outlier |
| Rollison et al. 2008 | • Case-control<br>• Delaware | 287/311 | EV<br>D<br>PY<br>AI<br>FB | EV<br>D<br>PY<br>AI<br>FB | 1 | — | — | 1 | 1 | 1 | 1 | 1 | — | — | — |
| Slattery et al. 2008 | • 4-CBCS<br>• Case-control<br>• Arizona, Colorado, New Mexico, and Utah | 2,400/2,473 | 1 | — | 1 | 1 | 1 | — | — | 1 | 1 | 1 | — | — | — |
| Young et al. 2009 | • OWHS and OWDHS<br>• Case-control<br>• Canada | 5,246/5,564 | — | 1 | 1 | — | — | — | — | — | 1 | 1 | — | — | — |
| Brown et al. 2010 | • Case-control<br>• California and Hawaii | 591/960 | 1 | — | 1 | 1 | 1 | 1 | 1 | — | 1 | — | — | — | — |
| Gibson et al. 2010 | • Case-control<br>• Manila, Philippines | 123/965 | 1 | — | 1 | — | — | — | — | — | — | — | 1 | — | — |
| Kaushal et al. 2010 | • Case-control<br>• Northeast India | 117/174 | 1 | — | 1 | — | — | — | — | — | — | — | 1 | 1 | — |

**Table 6.16*S* Continued**

| Study | Design/population | Analytic sample size | Type of referent group | | Meta-analysis categories | | | | | | | Design and analysis issues | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | No active-only | No active/no passive | Ever | Current | Former | Duration | Cigarettes/day | Pack-years | Age at initiation | Before/during first pregnancy | Small sample | Mixed referent or inadequate adjustment or proxy | Cut-point/outlier |
| Cerne et al. 2011 | • Case-control<br>• Ljubljana, Slovenia | 784/709 | 1 | — | 1 | 1 | — | — | 1 | — | — | — | — | 1 | — |
| DeRoo et al. 2011a | • Case-control<br>• Washington | 1,027/777 | 1 | — | — | — | — | — | — | — | — | 1 | — | — | — |

*Note*: Analytic sample size is based on sample size reported for the ever smoking or smoking status category; for case-control studies, n of cases/n of controls, and for cohort studies, n of cases of total cohort. Measures of smoking are reported by meta-analysis category for studies with only 1 type of referent group. Measures of smoking are reported by each referent group for studies reporting both types of referent groups. **4-CBCS** = 4–Corners Breast Cancer Study; **AI** = age at initiation; **Carolina BCS** = Carolina Breast Cancer Study; **CD** = cigarettes/day; **D** = duration; **ColBCS** = Collaborative Breast Cancer Study; **CTS** = California Teachers Study; **ER+** = estrogen receptor positive; **FB** = timing in relation to first pregnancy/first birth; **CLUE-II** = Campaign Against Cancer and Heart Disease; **EV** = ever; **GENICA** = Gene Environment Interaction and Breast Cancer in Germany; **IWHS** = Iowa Women's Health Study; **JCCS** = Japan Collaborative Cohort Study for Evaluation of Cancer Risk; **JPHC** = Japan Public Health Center based prospective study; **KBCS** = Kuopio Breast Cancer Study; **KPMCP** = Kaiser Permanente Medical Care Program; **LIBCSP** = Long Island Breast Cancer Study Project; **LSS-RERF** = Life-Span Study of the Radiation Effects Research Foundation; **MPCDRF** = Monitoring Project on Cardiovascular Disease Risk Factors; **MS** = Migrant Study (Norwegian Component); **MWS** = Million Women Study; **N-SWLHCS** = Norwegian-Swedish Women's Lifestyle and Health Cohort Study; **NBSS** = Canadian National Breast Screening Study; **NECSS** = National Enhanced Cancer Surveillance System; **NHS** = Nurses' Health Study; **OWHS** = Ontario Women's Health Study; **OWDHS** = Ontario Women's Diet and Health Study; **PY** = pack-years: the number of years of smoking multiplied by the number of packs of cigarettes smoked per day; **ST** = status (never, current, former); **TNBC** = triple negative breast cancer; **U.S.-RTS** = U.S. Radiologic Technologists Study; **WHI** = Women's Health Initiative Observational Study. Estimates were abstracted either directly or pooled using other measures of smoking to calculate an estimate for the appropriate category.

[a]Studies included in the pooled analysis restricted to nondrinkers conducted by the Collaborative Group on Hormonal Factors in Breast Cancer (Collaborative Group on Hormonal Factors in Breast Cancer et al. 2002). Smoking data was not provided in the publications cited and sample sizes are those provided in the collaborative report from the pooled analysis with the exception of 1 cohort study (Hiatt and Bawol 1984). This study was combined in the collaborative report with 3 other studies, and it is not possible to determine the individual sample sizes used in the pooled analysis based on 1,923 cases out of a combined cohort of 9,578 nondrinkers. The analytic sample size reported in the above table is based on each study and is the total number of cases out of the total cohort, regardless of drinking status.

[b]Indicates those reports that overlap with another report and which contribute to at least 1 meta-analysis. In the case of 1 cohort study (NHS-I) and 1 case-control study (ColBCS), 2 reports contributed to separate meta-analyses because they offered different measures (NHS-I: Egan et al., 2002 and Xue et al., 2011; ColBCS: Egan et al. 2003 and Ahern et al. 2009).

[c]Some data not included in meta-analyses when reported only as a continuous measure: Roddam et al. 2007 for duration, age at initiation and cigarettes/day.

[d]This study was excluded from the comparison of the no active/no passive referent group with the no-active only referent group, as it was deleted after the meta-analysis of ever smoking due to small sample size and insufficient covariate adjustment.

**Table 6.17*S* Summary of meta-analyses for measures of active cigarette smoking for all studies combined and stratified by study design, based on cohort studies published before 2012 and case-control studies published from 2000 to 2011**

| Measure of smoking | n | All studies: RR (95% CI) | Q test ($p_h$) | n | Cohort studies: RR (95% CI) | Q test ($p_h$) | n | Case-control studies: RR (95% CI) | Q test ($p_h$) |
|---|---|---|---|---|---|---|---|---|---|
| Ever[a] | 46 | 1.12 (1.07–1.17) | <.001 | 19 | 1.10 (1.07–1.13) | .793 | 27 | 1.15 (1.06–1.25) | <.001 |
| Ever[b] | 33 | 1.11 (1.06–1.16) | <.001 | 12 | 1.10 (1.07–1.13) | .717 | 21 | 1.13 (1.04–1.23) | <.001 |
| Ever[c] | 30 | 1.09 (1.06–1.12) | .500 | 11 | 1.10 (1.07–1.13) | .659 | 19 | 1.08 (1.03–1.13) | .340 |
| No-active only[d] | 25 | 1.09 (1.06–1.13) | .308 | 11 | 1.10 (1.07–1.14) | .720 | 14 | 1.08 (1.02–1.15) | .149 |
| No active/no passive[e] | 14 | 1.15 (1.09–1.21) | .572 | 4 | 1.16 (1.09–1.24) | .964 | 10 | 1.14 (1.02–1.28) | .282 |
| Former[f] | 25 | 1.09 (1.05–1.13) | .062 | 11 | 1.09 (1.03–1.14) | .021 | 14 | 1.09 (1.03–1.16) | .354 |
| Current[f] | 25 | 1.12 (1.08-1.16) | .347 | 11 | 1.14 (1.10–1.18) | .746 | 14 | 1.07 (1.00–1.16) | .209 |
| Duration, ≥20y[g] | 19 | 1.16 (1.12–1.21) | .318 | 7 | 1.15 (1.10–1.19) | .819 | 12 | 1.23 (1.12–1.36) | .146 |
| Duration, <20y[g] | 19 | 1.04 (1.01–1.07) | .922 | 7 | 1.04 (1.00–1.08) | .843 | 12 | 1.04 (0.97–1.12) | .751 |
| Cigarettes/day, ≥20[h] | 18 | 1.13 (1.09–1.17) | .903 | 8 | 1.12 (1.08–1.17) | .851 | 10 | 1.19 (1.06–1.33) | .756 |
| Cigarettes/day, <20[h] | 18 | 1.10 (1.06–1.16) | .031 | 8 | 1.07 (1.04–1.10) | .547 | 10 | 1.23 (1.11–1.37) | .033 |
| Pack-years, ≥20[i] | 16 | 1.16 (1.11–1.21) | .304 | 6 | 1.15 (1.10–1.19) | .346 | 10 | 1.21 (1.09–1.34) | .314 |
| Pack-years, <20[i] | 16 | 1.09 (1.03–1.15) | .099 | 6 | 1.04 (1.00–1.09) | .872 | 10 | 1.20 (1.05–1.37) | .023 |
| Age at smoking initiation, <20y[j] | 22 | 1.11 (1.07–1.16) | .088 | 8 | 1.09 (1.06–1.13) | .541 | 14 | 1.12 (1.02–1.22) | .029 |
| Age at smoking initiation, ≤16y[k] | 19 | 1.08 (1.00–1.15) | .065 | 7 | 1.09 (1.02–1.17) | .327 | 12 | 1.04 (0.92–1.17) | .053 |
| Age at smoking initiation, ≥20y[l] | 19 | 1.08 (1.05–1.12) | .673 | 8 | 1.07 (1.03–1.11) | .952 | 11 | 1.12 (1.04–1.19) | .291 |
| Smoking before/during first pregnancy[m] | 22 | 1.10 (1.04–1.17) | <.001 | 9 | 1.16 (1.12–1.20) | .746 | 13 | 1.05 (0.94–1.18) | .001 |

*Note:* **CI** = confidence interval; **n** = sample size (number of studies); **RR** = relative risk; **y** = years. Estimates were either abstracted directly or pooled using other measures of smoking to calculate an estimate for the appropriate category (Table 6.16*S* provides more details about which studies contributed to exposure categories and reasons for exclusions). Cochran's $\chi 2$ test, reported as the Q-test statistic, was used to assess between-study heterogeneity ($p_h$); $p_h$ values reported in SAS as 0.000 due to rounding shown in table as <0.001. Summary estimates for all meta-analyses are based on random effects models.

[a]Excludes 15 overlapping reports from 11 studies that were not the most recent or most complete report (Table 6.16*SA*) and 4 studies designed to evaluate smoking only before or during first pregnancy (Table 6.16*SB*), except for 2 meta-analyses. The estimates for the age at initiation meta-analysis were extracted from Egan and colleagues (2003) because estimates for age at initiation were not reported by Ahern and colleagues (2009). The estimates for the no active/no passive meta-analysis were extracted from Egan and colleagues (2002) rather than Xue and colleagues (2011), because the latter report used a no active-only referent group. See Figure 6.28 and 6.29.

[b]Excludes 19 reports (*note a*), 2 cohort studies reported in the pooled analysis restricted to nondrinkers (Collaborative Group on Hormonal Factors in Breast Cancer et al. 2002), 8 studies with <210 cases, and 3 studies with a mixed referent group or insufficient adjustment (Table 6.16*SB*).

[c]Excludes 32 reports (*note b*) and the remaining 3 studies with a design or analysis issue in Table 6.16B (Nordlund et al. 1997; Lash and Aschengrau 2002; Kruk 2007) (see Figure 6.30).

[d]Excludes 35 reports (*note c*) and 5 studies that did not have a no active-only referent group (Table 6.16*S*). See Figure 6.31.

[e]Excludes 35 reports (*note c*) and 16 studies that did not have a no active/no passive referent group (Table 6.16*S*). See Figure 6.32.

[f]Excludes 35 reports (*note c*) and 5 studies that did not have an estimate for former or current smoking (Table 6.16*S*). See Figures 6.33 and 6.34.

[g]Excludes 35 reports (*note c*), 1 study with a continuous measure only (Roddam et al. 2007), 10 studies with no available estimate for smoking duration (Hiatt and Fireman 1986; Hiatt et al. 1988; Manjer et al. 2000b; Gammon et al. 2004a; Sillanpaa et al. 2005a; Ha et al. 2007; Slattery et al. 2008; Ahern et al. 2009; Young et al. 2009; Andonova et al. 2010) (Table 6.16*S*). See Figure 6.35 for 20 or more years of smoking duration.

**Table 6.17*S* Continued**

[h]Excludes 35 reports (*note c*), 1 study with a continuous measure only (Roddam et al. 2007), 2 studies where the highest category was for less than 20 cigarettes/day (Gram et al. 2005; Lissowska et al. 2005), and 9 studies with no available estimate for cigarettes/day (Olson et al. 2005; Ahern et al. 2009; Sillanpaa et al. 2005a; Andonova et al. 2010; Kropp and Chang-Claude 2002; Ha et al. 2007; Prescott et al. 2007; Slattery et al. 2008; Young et al. 2009) (Table 6.16*S*). See Figure 6.36 for 20 or more cigarettes/day.
[i]Excludes 35 reports (*note c*), 1 study where the highest category was for five or more pack-years (Sillanpaa et al. 2005a), and 13 studies with no available estimate for pack-years (Hiatt and Fireman 1986; Hiatt et al. 1988; Manjer et al. 2000b; van der Hel et al. 2003b; Al-Delaimy et al. 2004; Lissowska et al. 2006; Mechanic et al. 2006; Ha et al. 2007; Prescott et al. 2007; Roddam et al. 2007; Young et al. 2009; Andonova et al. 2010; Brown et al. 2010) (Table 6.16*S*). See Figure 6.37 for 20 or more pack-years.
[j]Excludes 35 reports (*note c*), 1 study with a continuous measure only (Roddam et al. 2007), and 7 studies with no available estimate for age at initiation of smoking (Hiatt and Fireman 1986; Hiatt et al. 1988; Manjer et al. 2000b; Band et al. 2002; van der Hel et al. 2003b; Sillanpaa et al. 2005a; Andonova et al. 2010) (Table 6.16*S*). See Figure 6.38 for less than 20 years of age at smoking initiation.
[k]Excludes 43 reports (*note j*) and 3 studies that did not report a cutpoint of ≤16 years for age at initiation (Reynolds et al. 2004a, Li et al. 2005; Magnusson et al. 2007) (Table 6.16*S*B).
[l]Excludes 43 reports (*note j*) and 3 studies that did not report a cutpoint of ≥20 years for age at initiation (Gammon et al. 2004a; Rollison et al. 2008; Egan et al. 2003) (Table 6.16*S*B).
[m]Excludes the 15 overlapping reports (*note a*), 16 studies with a design or analysis issue and included in meta-analyses for only overall ever smoking (see Table 6.16*S*B), and 12 studies with no available estimate for smoking before first pregnancy (Hiatt and Fireman 1986; Hiatt et al. 1988; Manjer et al. 2000b; Johnson et al. 2000; Zheng et al. 2002a; van der Hel et al. 2003b; Sillanpaa et al. 2005a; Mechanic et al. 2006; Roddam et al. 2007; Ahern et al. 2009; Andonova et al. 2010; Brown et al. 2010) (Table 6.16*S*). See Figure 6.39.

**Table 6.18*S* Reports of premenopausal and postmenopausal relative risks (RRs) by study and meta-analysis RRs for the association of active smoking (ever, pack-years) with risk for breast cancer, based on cohort studies published before 2012 and case-control studies published from 2000 to 2011 (n = 20)**

**A. Cohort Studies (n = 6)**

| | | Ever smoking: RR (95% CI) | | Pack-years of smoking: RR (95% CI) | |
|---|---|---|---|---|---|
| **Study** | **Number of cases/total cohort** | **Premenopausal (n = 4)** | **Postmenopausal (n = 6)** | **Premenopausal (n = 2)** | **Postmenopausal (n = 4)** |
| Hiatt and Fireman, 1986[a] | 1,363/74,564 | 1.19 (1.03–1.38) | 1.17 (0.97–1.41) | — | — |
| Manjer et al. 2000b[b] | 416/10,902 | 1.35 (1.03–1.76) | 1.06 (0.85–1.33) | — | — |
| Reynolds et al. 2004b[a] | 2,005/116,544 | 1.10 (0.89–1.36) | 1.15 (0.96–1.38) | ≤10: 1.03 (0.78–1.35)<br>11–20: 1.31 (0.87–1.98)<br>21–30: 0.46 (0.17–1.24)<br>>30: 2.05 (1.20–3.49)<br>Pooled:[c] 1.03 (0.24–4.44) | ≤10: 1.02 (0.88–1.88)<br>11–20: 1.23 (1.02–1.50)<br>21–30: 1.13 (0.89–1.44)<br>>30: 1.19 (0.99–1.42)<br>Pooled:[c] 1.17 (1.01–1.35) |
| Olson et al. 2005[a] | 2,017/37,105 | — | 1.13 (1.03–1.24) | — | 1–19: 1.05 (0.91–1.21)<br>20–39: 1.18 (1.02–1.37)<br>>39: 1.15 (0.96–1.37)<br>Pooled:[c] 1.17 (1.04–1.31) |
| Luo et al. 2011b[a] | 3,520/79,990 | — | 1.10 (1.04–1.17) | — | <10: 1.04 (0.95–1.14)<br>10–19: 1.21 (1.08–1.36)<br>20–29: 1.13 (0.98–1.30)<br>30–39: 1.01 (0.86–1.19)<br>40–49: 1.16 (0.91–1.47)<br>>50: 1.18 (1.02–1.37)<br>Pooled:[c] 1.12 (1.03–1.21) |
| Xue et al. 2011[d] | 8,772/111,140 | 1.14 (1.04–1.24) | 0.91 (0.86–0.96) | 1–10: 1.01 (0.95–1.08)<br>11–20: 1.14 (1.06–1.22)<br>21–30: 1.15 (1.07–1.24)<br>>30: 1.27 (1.16–1.38)<br>Pooled:[c] 1.21 (1.09–1.33) | 1–5: 0.94 (0.86–1.02)<br>6–10: 0.89 (0.80–0.99)<br>11–15 0.90 (0.79–1.02)<br>>15 0.88 (0.79–0.99) |

**Table 6.18*S* Continued**

**B. Case-control studies (n = 14)**

| Study | Number of cases/controls | Ever smoking: RR (95% CI) | | Pack-years of smoking: RR (95% CI) | | | |
|---|---|---|---|---|---|---|---|
| | | Premenopausal (n = 13) | Postmenopausal (n = 11) | Premenopausal (n = 5) | | Postmenopausal (n = 6) | |
| Johnson et al. 2000[e] | 2,317/2,438 | 1.00 (0.80–1.30) | 1.20 (1.00–1.40) | 1–10:<br>11–20:<br>21–30:<br>>30:<br>**Pooled:[c]** | 2.40 (1.20–4.70)<br>2.30 (1.10–4.70)<br>1.70 (0.80–3.90)<br>1.50 (0.40–5.90)<br>**1.65 (0.83–3.26)** | 1–10:<br>11–20:<br>21–30:<br>>30:<br>**Pooled:[c]** | 1.40 (0.90–2.10)<br>1.20 (0.70–1.90)<br>1.90 (1.10–3.10)<br>1.60 (1.00–2.60)<br>**1.73 (1.22–2.46)** |
| Band et al. 2002 | 1,018/1,025 | 1.50 (1.09–2.07) | 0.96 (0.77–1.19) | <20:<br>≥20: | 1.30 (0.90–1.87)<br>1.69 (1.10–2.61) | <20:<br>≥20: | 0.84 (0.64–1.09)<br>1.03 (0.79–1.34) |
| Zheng et al. 2002a | 338/345 | 0.80 (0.50–1.40) | 1.20 (0.80–1.80) | <5:<br>5–20:<br>>20: | 0.80 (0.40–1.70)<br>1.00 (0.50–2.10)<br>0.40 (0.10–1.40) | <5:<br>5–20:<br>>20: | 1.10 (0.60–2.10)<br>1.30 (0.80–2.10)<br>1.20 (0.70–1.90) |
| Li et al. 2005 | 975/1,007 | — | 1.30 (1.00–1.50) | — | | <11:<br>11–27:<br>28–52:<br>>52:<br>**Pooled:[c]** | 1.00 (0.70–1.30)<br>1.40 (1.10–1.90)<br>1.30 (1.00–1.80)<br>1.30 (1.00–1.70)<br>**1.30 (1.07–1.58)** |
| Slattery et al. 2008[g] | 1,527/1,601 | 1.23 (0.99–1.53) | 1.00 (0.88–1.14) | See insert C | | | |
| Ahern et al. 2009[d] | 557/432 | 1.15 (0.63–2.12) | 1.05 (0.78–1.41) | 0–23:<br>>23: | 1.50 (0.90–2.40)<br>0.80 (0.40–1.60) | 0–23:<br>>23: | 1.10 (0.70–1.60)<br>1.00 (0.60–1.40) |
| Kropp and Chang-Claude 2002[f] | 468/1,093 | 1.31 (0.90–1.92) | — | — | | — | |
| Gammon et al. 2004a | 1,356/1,383 | 0.98 (0.54–1.78) | 1.08 (0.72–1.62) | — | | — | |
| Lissowska et al. 2006[h] | 2,386/2,502 | 1.95 (1.38–2.76) | 0.91 (0.77–1.09) | — | | — | |
| Kruk 2007[b] | 858/1,085 | 2.34 (1.81–3.02) | 1.76 (1.41–2.19) | — | | — | |
| Magnusson et al. 2007[i] | 3,345/3,454 | 1.40 (0.70–2.50) | 1.00 (0.90–1.20) | — | | — | |
| Prescott et al. 2007 | 1,728/441 | 0.99 (0.78–1.25) | — | — | | — | |
| Roddam et al. 2007[a] | 639/640 | 1.09 (0.90–1.33) | — | — | | — | |
| Rollison et al. 2008 | 287/311 | 1.53 (0.60–3.95) | 1.36 (0.95–1.94) | — | | — | |

**Table 6.18*S* Continued**

| Study | Number of cases/controls | Ever smoking: RR (95% CI) | | Pack-years of smoking: RR (95% CI) | |
|---|---|---|---|---|---|
| | | Premenopausal (n = 13) | Postmenopausal (n = 11) | Premenopausal (n = 5) | Postmenopausal (n = 6) |
| Cohort studies RR | — | 1.16 (1.08–1.24) | 1.07 (0.97–1.19) | 1.21 (1.10–1.34) | 1.08 (0.95–1.23) |
| Case-control studies RR | — | 1.30 (1.04–1.62) | 1.13 (1.01–1.27) | 1.23 (0.84–1.80) | 1.18 (1.01–1.38) |
| Exclusion of outlier[j] | | 1.20 (1.02–1.42) | 1.07 (0.98–1.16) | — | — |
| All studies RR | — | 1.26 (1.11–1.43) | 1.10 (1.02–1.19) | 1.24 (1.03–1.49) | 1.12 (1.02–1.23) |
| Exclusion of outlier[j] | | 1.18 (1.08–1.29) | 1.07 (1.00–1.14) | — | — |

*Note:* One study reported data for pack-years, but estimates were restricted to parous women only and are not included in this table (Ha et al. 2007). Direct nonpooled estimates for ever smoking for the following studies: (Johnson et al. 2000; Band et al. 2002; Kropp and Chang-Claude 2002; Zheng et al. 2002a; Gammon et al. 2004a; Li et al. 2005; Lissowska et al. 2006; Magnusson et al. 2007; Prescott et al. 2007; Rollison et al. 2008). None of the summary estimates shown was associated with a statistically significant result for publication bias using the Begg or Egger statistic (p ≥0.05). Results for the Q-test for heterogeneity are not shown in the table.
**CI** = confidence interval; **H** = Hispanic; **NHW** = non-Hispanic White.
[a]Summary estimate for ever smoking pooled from estimates for former and current smokers reported within menopausal status (Hiatt and Fireman 1986; Reynolds et al. 2004a; Olson et al. 2005; Roddam et al. 2007; Luo et al. 2011b).
[b]Summary estimate for ever smoking pooled from estimates for levels of cigarettes/day within menopausal status (Kruk 2007; Manjer et al. 2000b).
[c]Estimates for categories of pack-years ≥20 pooled for meta-analysis.
[d]Summary estimate for ever smoking pooled from estimates for levels of pack-years reported within menopausal status (Ahern et al. 2009; Xue et al. 2011). The estimates for pack-years reported in Xue and colleagues (2011) are defined as pack-years from menarche to before menopause (premenopausal); and pack-years after menopause (postmenopausal).
[e]The estimates for ever smoking are based on the full study sample using no-active only as the referent group. However, the estimates for pack-years are based on the subsample using the no active/no passive exposure referent group for those reporting a lifetime residential smoking history of >90%, which reduces the total sample size by 38%. Estimates for pack-years were not available for the no-active only referent group (Johnson et al. 2000).
[f]Approximately 80% of the study population was premenopausal; approximately 13-16% classified as menopause unknown (Kropp and Chang-Claude 2002).
[g]Summary estimates for ever smoking pooled across estimates for non-Hispanic White and Hispanic women within menopausal status; estimates for pack-years pooled across ethnicity for both 1–15 and >15 pack-years (Slattery et al. 2008).
[h]Estimate for premenopausal, based on women <45 years of age; estimate for postmenopausal, based on women >55 years of age; estimate for women 45–55 years of age excluded (Lissowska et al. 2006).
[i]The estimates by menopausal status are based on current smokers compared to never smokers; former smokers appear to be excluded. The majority of women were postmenopausal (age range: 50–74 years). The exact percent for premenopausal women could not be determined (Magnusson et al. 2007).
[j]The exclusion of the outlier estimate reported for the study by Kruk (2007).

**Table 6.19*S*** **Reports of estrogen receptor status relative risks (RRs) for the association of active cigarette smoking (ever, cigarettes/day) with risk for breast cancer, based on cohort studies published before 2012 and case-control studies published from 2000 to 2011 (n = 17)**

**A. Cohort studies (n = 2)**

| Study | Age group and location | Sample size of cases (% with ER) | Ever smoking: RR (95% CI) | | Cigarettes/day: RR (95% CI) | |
|---|---|---|---|---|---|---|
| | | | ER+ | ER– | ER+ | ER– |
| London et al. 1989[a] | 30–55 years of age<br>United States | 1,788 (50) | 1.18 (1.04–1.35) | 1.01 (0.82–1.24) | 1–14: 1.13 (0.82–1.54)<br>15–24: 1.08 (0.82–1.43)<br>≥25: 1.38 (1.04–1.84) | 1–14: 0.68 (0.41–1.12)<br>15–24: 1.15 (0.81–1.63)<br>≥25: 1.05 (0.69–1.59) |
| Al-Delaimy et al. 2004[b] | 25–42 years of age<br>United States | 785 (78) | 1.30 (1.13–1.51) | 1.07 (0.86–1.34) | 1–4: 1.45 (1.09–1.93)<br>5–14: 1.46 (1.14–1.87)<br>15–24: 1.06 (0.81–1.38)<br>≥25: 1.16 (0.64–2.09) | 1–4: 0.62 (0.14–2.71)<br>5–14: 1.14 (0.78–1.68)<br>15–24: 1.23 (0.86–1.75)<br>≥25: 0.99 (0.50–1.93) |

**B. Case-control studies (n = 15)**

| Study | Age group and location | Sample size of cases (% with ER) | Ever smoking: RR (95% CI) | | Cigarettes/day: RR (95% CI) | |
|---|---|---|---|---|---|---|
| | | | ER+ | ER– | ER+ | ER– |
| Luo et al. 2011b[c] | 50–79 years of age<br>United States | 3,520 (89) | 1.15 (1.07–1.23) | 1.00 (0.83–1.19) | — | — |
| McTiernan et al. 1986[d] | 25–54 years of age<br>United States | 329 (73) | 1.03 (0.73–1.47) | 0.79 (0.52–1.20) | — | — |
| Stanford et al. 1987 | 20–54 years of age<br>United States | 561 (82) | 1.03 (0.70–1.40) | 1.00 (0.70–1.40) | — | — |
| Cooper et al. 1989 | 20–74 years of age<br>Australia | 451 (84) | 0.95 (0.66–1.37) | 1.63 (1.00–2.66) | — | — |
| Yoo et al. 1997 | ≥25 years of age<br>Japan | 1,154 (40) | 1.42 (1.04–1.94) | 1.33 (0.87–2.02) | — | — |
| Morabia et al. 1998[e] | 30–74 years of age<br>Switzerland | 264 (92) | 2.28 (1.56–3.35) | 4.01 (1.90–8.46) | <20: 2.20 (1.30–3.60)<br>≥20: 2.40 (1.40–4.50) | <20: 3.80 (1.40–10.3)<br>≥20: 4.30 (1.40–13.2) |
| Huang et al. 2000a[d] | 20–74 years of age<br>United States | 862 (91) | 1.10 (0.84–1.45) | 0.86 (0.48–1.54) | — | — |
| Manjer et al. 2001[d] | 50 years of age<br>Sweden | 268 (100) | 0.94 (0.74–1.21) | 2.41 (1.57–3.71) | ≤19: 0.87 (0.60–1.25)<br>≥20: 0.82 (0.49–1.39) | ≤19: 2.04 (1.07–3.88)<br>≥20: 2.62 (1.17–5.87) |

**Table 6.19*S* Continued**

| Study | Age group and location | Sample size of cases (% with ER) | Ever smoking: RR (95% CI) | | Cigarettes/day: RR (95% CI) | |
|---|---|---|---|---|---|---|
| | | | ER+ | ER– | ER+ | ER– |
| Britton et al. 2002[f] | 20–44 years of age<br>United States | 1,556 (78) | 0.87 (0.65–1.17) | 0.94 (0.78–1.33) | — | — |
| Cotterchio et al. 2003[g] | 25–74 years of age<br>Canada | 3,748 (87) | 1.08 (0.94–1.25) | 1.21 (0.94–1.56) | — | — |
| Gammon et al. 2004a[h] | 24–98 years of age<br>United States | 894 (66) | 1.17 (0.92–1.48) | 1.06 (0.75–1.51) | — | — |
| Li et al. 2005[i] | 65–79 years of age<br>United States | 900 (92) | 1.22 (1.02–1.46) | 1.30 (0.80–2.00) | <10: 1.27 (0.97–1.68)<br>10–19: 1.22 (0.95–1.57)<br>≥20: 1.20 (0.96–1.51) | <10: 1.00 (0.50–2.00)<br>10–19: 2.00 (1.10–3.50)<br>≥20: 1.10 (0.60–2.00) |
| Lissowska et al. 2006[j] | Poland<br>20–74 years of age | 1,716 (72) | 1.16 (0.99–1.36) | 1.04 (0.86–1.27) | <10: 1.06 (0.82–1.37)<br>10–14: 1.26 (0.99–1.60)<br>>14: 1.02 (0.81–1.29) | <10: 1.07 (0.77–1.48)<br>10–14: 1.13 (0.84–1.53)<br>>14: 0.73 (0.73–1.32) |
| Trivers et al. 2009[k] | 20–54 years of age<br>United States | 831 (57) | 0.98 (0.51–1.91) | 1.22 (0.67–2.22) | — | — |
| Rabstein et al. 2010[d] | <80 years of age<br>Germany | 1,020 (75) | 0.79 (0.65–0.95) | 1.12 (0.84–1.49) | — | — |

*Note:* **CI** = confidence interval; **ER** = estrogen receptor; **HER2** = human epidermal growth factor receptor 2; **PR** = progesterone receptor.
[a]Estimates for ex-smokers and for categories of cigarettes/day among current smokers pooled for an estimate of ever smoking (London et al. 1989).
[b]Estimates for the four categories of duration pooled for an estimate of ever smoking (Al-Delaimy et al. 2004).
[c]Estimates for current and former smoking pooled across ER/PR status for an estimate of ever smoking (Luo et al. 2011b). Overlaps with an analysis restricted to an evaluation of triple negative (n = 300) and ER+ (n = 2,479) (Kabat et al. 2011) (See Table 6.16*S* in this report).
[d]Estimates for current and former smoking pooled for an estimate of ever smoking (McTiernan et al. 1986; Huang et al. 2000a; Manjer et al. 2001; Rabstein et al. 2010).
[e]Estimates for levels of numbers of cigarettes/day among ever smokers pooled for an estimate of ever smoking (Morabia et al. 1998).
[f]Estimates for current and former smoking pooled across PR categories for an estimate of ever smoking (Britton et al. 2002).
[g]Estimates for pack-years pooled across menopausal status pooled for an estimate of ever smoking (Cotterchio et al. 2003). Discordant ER/PR results were not included in the manuscript.
[h]Estimates for active smoking only and passive and active smoke exposure pooled across PR categories for an estimate of ever smoking. Referent group based on no active/no passive exposure (Gammon et al. 2004a).
[i]Estimates for ever smokers pooled across PR categories (ER+/PR+, ER+/PR-) to calculate an estimate for ever smoking by ER+ status; (ER–/PR+) did not have a calculated estimate as there were only 6 cases (Li et al. 2005).
[j]CI for >14 cigarettes/day for ER– status appears to have a typographical error (Lissowska et al. 2006).
[k]Estimates for current and former smoking pooled across ER/PR/HER2 status for an estimate of ever smoking (Trivers et al. 2009).

**Table 6.20*S* Reports on the association between active cigarette smoking and risk of a second primary contralateral breast cancer (n = 7)**

| Study | Design/population | Cases/noncases | Measure of smoking: RR (95% CI) |
|---|---|---|---|
| Kato et al. 1986[a] | • Case control<br>• 1964–1984<br>• 49 years of age<br>• Japan | 115/230 | ≥10 cigarettes/day: 0.41 (p = 0.05) |
| Horn and Thompson 1988[b] | • Case control<br>• 1975–1983<br>• 20–93 years of age<br>• 8 hospitals<br>• Connecticut | 292/264 | Ever: 0.8 (0.5–1.3)<br>≥40 years duration: 1.5 (0.7–3.2)<br>≥1 pack/day: 1.7 (0.9–3.1)<br>≥40 pack-years: 1.5 (0.7–3.2) |
| Bernstein et al. 1992[b] | • Cohort<br>• Cancer and Steroid Hormone Study (8 SEER sites)<br>• 1980–1982<br>• 20–54 years of age | 136/4,550 | Ever: 1.24 (0.87–1.77)<br><19 years of age at smoking initiation: 1.24 (0.80–1.92) |
| Fowble et al. 2001[c] | • Cohort<br>• 1978–1994<br>• 22–88 years of age<br>• Pennsylvania | 87/1,253 | Ever: ~0.5 (p = 0.04) |
| Trentham-Dietz et al. 2007a[b] | • Cohort<br>• 1987–2000<br>• 18–79 years of age<br>• Wisconsin | 488/10,953 | Current: 1.00 (0.78–1.28)<br>Former: 1.09 (0.89–1.35) |
| Knight et al. 2009[d] | • Case control<br>• WECARE<br>• 1985–2001<br>• <55 years of age<br>• Iowa, Los Angeles and Orange County in California, Seattle, Denmark | 708/1,399 | Ever: 1.1 (0.9–1.6)<br>Ever, risk period: 1.2 (0.9–1.5)<br>≥20 years duration: 1.1 (0.9–1.5)<br>>0.5 packs/day (mean): 1.1 (0.8–1.4)<br>19 pack-years: 1.1 (0.8–1.4)<br><20 years of age at smoking initiation: 1.1 (0.9–1.4) |
| Li et al. 2009[e] | • Nested case control<br>• 1990–2005<br>• 40–79 years of age<br>• Seattle-Puget Sound<br>• 4 counties in Western Washington | 365/726 | Current, baseline: 1.8 (1.1–3.2)<br>Current, reference: 2.2 (1.2–4.0) |

*Note:* **CI** = confidence interval; **pack-years** = the number of years of smoking multiplied by the number of packs of cigarettes smoked per day; **RR** = relative risk; **SEER** = Surveillance, Epidemiology, and End Results Program; **WECARE** = Women's Environmental Cancer and Radiation Epidemiology Study.

[a]Ascertained from women identified through a cancer clinic; no information on stage is provided. The referent group for measure of smoking is based on women who smoked <10 cigarettes/day.

[b]Ascertained from women identified through either the state cancer registry (Horn and Thompson 1988; Trentham-Dietz et al. 2007a) or through the SEER Program (Bernstein et al. 1992) and diagnosed with a first primary breast cancer (controls) or a second primary breast cancer diagnosed in the contralateral breast (cases).

[c]Ascertained from women identified through clinics with Stage I–II breast cancer over a median follow-up time of 8.9 years. Rate ratio calculated for this table based on cumulative incidence for smokers = 5% and 10% for nonsmokers at 10-year follow-up. Missing data for smoking history for 38% of subjects.

[d]Ascertained from women identified through population-based cancer registries with either a first primary invasive breast cancer with no regional lymph node involvement (controls) or a second primary in situ or invasive breast cancer diagnosed in the contralateral breast no more than 1 year after the first breast cancer diagnosis (cases). The referent group was never smokers for all categories with the exception of 'Ever, risk period', which was defined as starting prior to or during the period between the first diagnosis and the reference date and stopping during or after this period.

[e]Ascertained from women identified through a population-based cancer registry with Stage I–IIIB and ER+ breast cancer; baseline = first breast cancer diagnosis; reference = date of contralateral breast cancer diagnosis for cases and for controls the date of the matched patient's contralateral diagnosis.

**Table 6.21*S* Modification of risk for breast cancer associated with smoking by *NAT2* phenotype, based on two meta-analyses and one pooled analysis, stratified by menopausal status**

| | | Slow acetylation status | | | Fast acetylation status | | |
|---|---|---|---|---|---|---|---|
| **Study** | **Measure of smoking** | **All women: RR (95% CI)** | **Premenopausal: RR (95% CI)** | **Postmenopausal: RR (95% CI)** | **All women: RR (95% CI)** | **Premenopausal: RR (95% CI)** | **Postmenopausal: RR (95% CI)** |
| Terry and Goodman 2006[a] | | 1.50 (1.20–1.80) | 1.40 (0.90–2.20) | 2.40 (1.70–3.30) | 1.20 (1.00–1.50) | 1.50 (0.90–2.40) | 1.30 (0.80–2.00) |
| Ambrosone et al. 2008[b] | Ever smoking | 1.27 (1.16–1.40) $p_h = 0.30$[c] | 1.28 (1.09–1.50) $p_h = 0.89$ | 1.34 (1.17–1.53) $p_h = 0.39$ | 1.05 (0.95–1.17) $p_h = 0.61$ | 1.08 (0.89–1.30) $p_h = 0.26$ | 1.07 (0.92–1.24) $p_h = 0.51$ |
| | <20 pack-years | 1.21 (1.08–1.35) | 1.21 (1.00–1.45) | 1.28 (1.08–1.50) | 1.06 (0.93–1.21) | 1.00 (0.80–1.24) | 1.12 (0.93–1.36) |
| | ≥20 pack-years | 1.44 (1.23–1.68) | 1.47 (1.08–2.01) | 1.41 (1.15–1.72) | 1.04 (0.87–1.25) | 1.34 (0.94–1.89) | 0.98 (0.77–1.26) |
| Cox et al. 2011[d] | Duration (years), continuous | 1.01 (1.00–1.01) | 1.00 (0.99–1.01) | 1.01 (1.00–1.01) | 1.01 (1.00–1.01) | 1.00 (0.99–1.01) | 1.00 (1.00–1.01) |
| | Pack-years, continuous | 1.01 (1.00–1.01) | 1.00 (0.99–1.01) | 1.01 (1.00–1.01) | 1.01 (1.00–1.01) | 1.00 (0.99–1.01) | 1.01 (1.00–1.01) |
| | ≤15 years duration | 1.07 (0.95–1.21) | — | — | 1.14 (0.98–1.32) | — | — |
| | >15 years duration | 1.18 (1.07–1.29) | — | — | 1.17 (1.04–1.30) | — | — |
| | ≤20 pack-years | 1.08 (0.92–1.19) | — | — | 1.13 (1.01–1.27) | — | — |
| | >20 pack-years | 1.25 (1.11–1.39) | — | — | 1.24 (1.08–1.42) | — | — |

*Note:* **CI** = confidence interval; **RR** = relative risk.

[a]Ever smokers compared with never smokers for 13 studies (4,837 cases, 6,017 controls). (Ambrosone et al. 1996; Hunter et al. 1997; Millikan et al. 1998; Delfino et al. 2000; Morabia et al. 2000; Krajinovic et al. 2001; Chang-Claude et al. 2002; Egan et al. 2003; van der Hel et al. 2003b; Alberg et al. 2004; Lilla et al. 2005; van der Hel et al. 2005; Sillanpaa et al. 2005a).

[b]Referent group based on never smokers. Acetylator status based on common use across studies: rapid equals presence of one rapid acetylator allele, and slow equals presence of three common variant alleles (*NAT2*5, NAT2*6,* and *NAT2*7*). Summary estimates for ever smokers based on 13 studies (6,757 cases, 7,454 controls) (Ambrosone et al. 1996; Hunter et al. 1997; Millikan et al. 1998; Morabia et al. 2000; Krajinovic et al. 2001; Chang-Claude et al. 2002; Egan et al. 2003; van der Hel et al. 2003b; Alberg et al. 2004; Kocabas et al. 2004; van der Hel et al. 2005; Sillanpaa et al. 2005a; Lissowska et al. 2006). Estimates for pack-years based on 8 studies (Ambrosone et al. 1996; Morabia et al. 2000; Chang-Claude, et al. 2002; Egan et al. 2003; van der Hel et al. 2003b; Alberg et al. 2004; Sillanpaa et al. 2005a; Lissowska et al. 2006). There was no significant heterogeneity across studies for pack-years. Summary estimates, independent of acetylator status: <20 pack-years (RR = 1.14; 95% CI, 1.03–1.25); ≥20 pack-years (RR = 1.26; 95% CI, 1.12–1.43).

[c]$p_h$ for heterogeneity.

[d]Based on a pooled analysis of nested case-control studies from 7 cohorts (6,900 cases, 9,903 controls). Fast acetylation status is based on the combination of rapid plus intermediate phenotypes.

**Table 6.22*S* Reports on cohort studies of the association between exposure to secondhand smoke and relative risk (RR) for breast cancer incidence, based on studies published before 2012 included in the 2006 Surgeon General's Report (n = 7)**

| Study | Design/population | Number of breast cancer events | Data collection/subgroup analyses | Findings for exposure to secondhand smoke | Measures of exposure to secondhand smoke: RR (95% CI) | Confounders |
|---|---|---|---|---|---|---|
| Gram et al. 2005 | • Women's Lifestyle and Health Study Norwegian-Swedish Cohort<br>• 102,098 women were enrolled in 1991–1992 to evaluate lifestyle risk factors for multiple health outcomes<br>• Average follow-up: 8–9 years<br>• Ages 30–50 years<br>• Norway and Sweden | Approximately 377 incident cases (invasive) among 36,773 never active smokers (estimate for case number derived from the incidence for never smokers, 114/100,000 person-years, and total number of never smokers 36,773, assuming 9 years of followup) | • Self-administered questionnaire at enrollment<br>• Data collected from never smokers who reported having lived with a smoker or lived with a smoker during childhood<br>• Data collected for active cigarette smoking (see Table 6.14*S*) | • Nonsignificant increased risk for breast cancer among subjects ever exposed to passive smoke<br>• Nonsignificant results reported for different combinations of exposure during childhood and adulthood (data not provided) | **Ever in Lifetime:**<br>NA/NP: 1.00<br>Passive, ever: 1.21 (0.98–1.50) | Controlled for age at enrollment, menopausal status, number of children, age at birth of first child, HRT, use of oral contraceptives, BMI, alcohol use |
| Lin et al. 2008 | • Collaborative Cohort Study for Evaluation of Cancer Risk<br>• 34,401 women enrolled from 1988 to 1990 from 24 areas<br>• Average follow-up: 11–13 years<br>• Ages 40–79 years<br>• Japan | 140–178 incident cases (stage not specified), depending on the location of exposure to secondhand smoke, among 32,023 never smokers | • Self-administered questionnaire at enrollment.<br>• Data collected from nonsmokers exposed at home and in public, (1–2, 3–4 days/week, almost every day), and exposure during childhood.<br>• Data collected for active cigarette smoking (see Table 6.14*S*) | • No association between risk for breast cancer and exposure at home or outside the home<br>• Small but nonsignificant increase in risk for exposure during childhood<br>• No association when analyses were based on referent group composed of nonsmokers that had no exposure to secondhand smoke at home or in public places | **Adulthood, household:**<br>NA/NP: 1.00<br>Sometimes: 0.59 (0.33–1.05)<br>Almost daily: 0.71 (0.48–1.05)<br>**Adulthood, public places:**<br>NA/NP: 1.00<br>Sometimes: 0.77 (0.51–1.15)<br>Almost daily: 0.84 (0.51–1.40)<br>**Childhood:**<br>NA/NP: 1.00<br>Yes: 1.24 (0.84–1.85) | Controlled for age, geographic area, BMI, family history, alcohol use, daily walking, age at menarche, age at birth of first child, menopausal status, parity, and HRT |

**Table 6.22*S* Continued**

| Study | Design/population | Number of breast cancer events | Data collection/subgroup analyses | Findings for exposure to secondhand smoke | Measures of exposure to secondhand smoke: RR (95% CI) | Confounders |
|---|---|---|---|---|---|---|
| Pirie et al. 2008 | • Million Women Study<br>• 224,917 women who reported being never smokers and enrolled in 66 breast cancer screening clinics from 1996 to 2001 to evaluate the association between exposure to passive smoke and breast cancer<br>• Average follow-up: 3.5 years<br>• Ages 50–64 years<br>• United Kingdom | 2,344 incident cases (invasive) among 210,647 never active smokers with complete data | • Self-administered questionnaire at enrollment<br>• Data collected for exposure to maternal or paternal smoking at birth, at age 10, and from partner | • No association between risk for breast cancer and exposure to secondhand smoke during childhood or adulthood or combined | **Childhood:**<br>NA/NP: 1.00<br>Birth: 0.98 (0.89–1.07)<br>Age 10: 0.96 (0.88–1.06)<br>**Childhood, maternal:**<br>NA/NP: 1.00<br>Birth or age 10: 0.96 (0.88–1.05)<br>**Childhood, paternal:**<br>NA/NP: 1.00<br>Birth or age 10: 1.03 (0.93–1.14)<br>**Childhood, both parents:**<br>NA/NP: 1.00<br>Birth or age 10: 1.00 (0.91–1.10)<br>**Adulthood:**<br>NA/NP: 1.00<br>Yes: 1.02 (0.89–1.16)<br>**Child and adulthood:**<br>NA/NP: 1.00<br>Yes: 1.03 (0.90–1.19)<br>**Child or adulthood:**<br>NA/NP: 1.00<br>Yes: 0.98 (0.88–1.09) | Controlled for age, region of residence, socioeconomic group, age at menarche, parity, age at birth of first child, menopausal status, BMI, physical activity, alcohol use, and HRT |

**Table 6.22*S* Continued**

| Study | Design/population | Number of breast cancer events | Data collection/subgroup analyses | Findings for exposure to secondhand smoke | Measures of exposure to secondhand smoke: RR (95% CI) | Confounders |
|---|---|---|---|---|---|---|
| Reynolds et al. 2009[a] | • California Teachers Study<br>• 329,000 women enrolled from 1995 to 2000 to evaluate risk factors for breast cancer<br>• Average follow-up: 12 years<br>• Age >20 years<br>• United States | 1,754 incident cases (invasive) among 57,523 never active smokers | • Self-administered questionnaire at time of enrollment and during Wave II in 1997.<br>• Data collected for exposure at home, work, and social settings during childhood (age <20 years) and/or adulthood (age ≥20 years), including variables for duration (sum of years across all settings) and intensity.<br>• Subgroups evaluated and stratified by menopausal status, family history of breast cancer, and estrogen receptor status (data not shown) | • No significant associations among lifetime passive exposure and risk of breast cancer<br>• Results not significant when evaluated by menopausal status and duration<br>• Risk was statistically significant only in postmenopausal women exposed in adulthood (age >20 years) with the highest intensity-years of exposure (RR = 1.25; 95% CI, 1.01–1.56) | **Ever:**<br>NA/NP: 1.00<br>Ever Passive: 1.10 (0.94–1.30)<br>**Ever, premenopausal:**<br>NA/NP: 1.00<br>Ever Passive: 1.04 (0.79–1.38)<br>**Ever, postmenopausal:**<br>NA/NP: 1.00<br>Ever Passive: 1.22 (0.97–1.52)<br>**Childhood:**<br>NA/NP: 1.00<br>Any: 1.06 (0.94–1.19)<br>**Adulthood:**<br>NA/NP: 1.00<br>Any: 1.04 (0.91–1.19)<br>Any Work: 1.02 (0.93–1.13)<br>**Duration (years):**<br>NA/NP: 1.00<br>Low (≤15): 1.10 (0.92–1.32)<br>Medium (15–30): 1.10 (0.92–1.32)<br>High (>30): 1.12 (0.93–1.33) | Controlled for age, race, family history, age at menarche, pregnancy history, lifetime duration of breastfeeding, physical activity, alcohol use, BMI, menopausal status, and HRT |
| Chuang et al. 2011 | • EPIC<br>• Women and men recruited from 23 centers in 10 countries in Europe to investigate risk factors for cancer from 1992 to 1998<br>• Average follow-up: 10 years<br>• Ages 25–70 years<br>• Europe | 3,187 incident cases (invasive) among 92,956 never active smoking women | • In-person or self-administered interviews were conducted depending on each center.<br>• Data collected for exposure during childhood and for frequency of exposure from French and Italian centers only. | • No significant association between breast cancer and passive smoke exposure in childhood. | **Status:**<br>NA/NP: 1.00<br>Yes: 0.98 (0.91–1.06)<br>**Frequency:**<br>NA/NP: 1.00<br>Few times/week: 0.98 (0.88–1.10)<br>Daily: 1.06 (0.95–1.19)<br>p-trend: 0.40 | Controlled for education, baseline alcohol use, BMI, physical activity, vegetable intake, fruit intake, nonalcoholic energy intake, adult passive smoking, age at menarche, use of oral contraceptives, parity, and menopausal status |

**Table 6.22*S* Continued**

| Study | Design/population | Number of breast cancer events | Data collection/subgroup analyses | Findings for exposure to secondhand smoke | Measures of exposure to secondhand smoke: RR (95% CI) | Confounders |
|---|---|---|---|---|---|---|
| Luo et al. 2011b[a] | • Women's Health Initiative Observational Study<br>• 93,676 women enrolled in 40 United States clinical centers from 1993 to 1998 to evaluate major causes of morbidity and mortality among postmenopausal women<br>• Average follow-up; 10.3 years<br>• Ages 50–79 years<br>• United States | 1,692 incident cases (invasive) among 41,022 never active smokers | • Self-administered questionnaire at enrollment.<br>• Data collected for exposure during childhood (<18 years), adulthood at home and at work, and duration of exposure<br>• Data for exposure to active smoking collected (see Table 6.14*S*)<br>• Subgroups evaluated and stratified by hormone receptor status and histology (ductal and lobular) | • No significant association between breast cancer and passive smoke exposure, except in the highest combined category of exposure (RR = 1.32; 95% CI, 1.04–1.67) based on exposure in childhood ≥10 years plus adult at home ≥20 years plus adult at work ≥10 years<br>• No significant dose response observed for any combination of time period and place.<br>• No significant association between risk and hormone receptor status or histologic type of breast cancer was observed | **Ever:**<br>NA/NP: 1.00<br>Any: 1.09 (0.92–1.29)<br>**Childhood:**<br>NA/NP: 1.00<br>Yes: 1.19 (0.93–1.53)<br>**Adulthood:**<br>NA/NP: 1.00<br>Home only: 0.91 (0.70–1.19)<br>Work only: 1.01 (0.82–1.26)<br>Home and work: 1.15 (0.93–1.41)<br>**Childhood and adulthood:**<br>NA/NP: 1.00<br>Home only: 1.04 (0.83–1.30)<br>Work only: 1.17 (0.94–1.45)<br>Home and work: 1.11 (0.92–1.34) | Controlled for age at enrollment, ethnicity, education, BMI, physical activity, alcohol use, parity, family history, history of HRT, age at menarche, and age of first live birth |

**Table 6.22*S* Continued**

| Study | Design/population | Number of breast cancer events | Data collection/subgroup analyses | Findings for exposure to secondhand smoke | Measures of exposure to secondhand smoke: RR (95% CI) | Confounders |
|---|---|---|---|---|---|---|
| Xue et al. 2011[a] | • Nurses' Health Study<br>• 121,700 registered nurses completed a mailed questionnaire in 1976 for information about factors related to breast cancer incidence and cardiovascular disease<br>• 78,206 women were followed prospectively for 14 years (1976–2006)<br>• Ages 30–55 years<br>• United States | 2,890 incident cancer cases (invasive) among 36,017 nonsmokers who completed the 1982 questionnaire | • Self-administered questionnaire at enrollment<br>• Data collected for parental smoking, duration, and frequency of exposure in adulthood at home and work<br>• Data collected for exposure to active smoking (see Table 6.14*S*)<br>• Subgroups evaluated and stratified by menopausal status | • No association between breast cancer and any measure of exposure to passive smoke<br>• No significant trend for duration of exposure or combination of duration and frequency | **Childhood:**<br>NA/NP: 1.00<br>Mother only: 0.83 (0.66–1.05)<br>Father only: 1.01 (0.93–1.10)<br>Both parents: 0.90 (0.79–1.03)<br>**Adulthood, work:**<br>NA/NP: 1.00<br>Occasionally: 0.99 (0.89–1.09)<br>Regularly: 0.87 (0.78–0.98)<br>**Adulthood, home:**<br>NA/NP: 1.00<br>Occasionally: 1.06 (0.97–1.17)<br>Regularly: 1.02 (0.90–1.14)<br>**Years living with smoker:**<br>NA/NP (<1): 1.00<br>1–4: 1.09 (0.96–1.24)<br>5–9: 0.98 (0.84–1.13)<br>10–19: 0.96 (0.86–1.08)<br>20–29: 0.96 (0.85–1.08)<br>30–39: 0.97 (0.84–1.13)<br>≥40: 0.99 (0.74–1.32)<br>p-trend: 0.24 | Controlled for age, family history, history of benign breast disease, current BMI and at age 18 years, height, alcohol use, age at menarche, parity, age at first birth, physical activity, use of oral contraceptives, menopausal status, postmenopausal HRT, and age at menopause; mutual adjustment for passive smoking at home and at work |

*Note:* Data from cohort studies for active cigarette smoking are summarized in Table 6.14*S*. Numbers for cases and controls are based on nonsmokers, which is a smaller percentage of subjects than the total included for analyses of active cigarette smoking. All results reported by the study may not appear in the summary table. **BMI** = body mass index; **CI** = confidence interval; **EPIC** = European Prospective Investigation into Cancer and Nutrition; **HRT** = hormone replacement therapy; **NA/NP** = no active/no passive.

[a]Overlapping reports based on the same study population.

**Table 6.23*S* Reports on case-control studies of the association between exposure to secondhand smoke and relative risk for breast cancer incidence, based on studies published before 2012 but not included in the 2006 Surgeon General's Report (n = 11)**

| Study | Design/population | Data collection/ subgroup analyses | Findings for exposure to secondhand smoke | Measures of exposure to secondhand smoke: RR (95% CI) | Confounders |
|---|---|---|---|---|---|
| Alberg et al. 2004 | • Nested case-control study to evaluate *NAT2* genotype and cigarette smoking on breast cancer risk within the Campaign against Cancer and Stroke (CLUE II) cohort designed to evaluate cancer and heart disease in 14,625 women<br>• 1989 baseline<br>• Mean age: 60 years<br>• 62 incident nonsmoker cases (stage not specified) from a total of 115 ascertained by Washington County Cancer Registry and Washington County Hospital<br>• 66 nonsmokers from a total of 115 controls matched on age (±1 year), race, menopausal status, and date of blood collection (115 total controls)<br>• Washington County, Maryland | • In-person interview<br>• Self-administered questionnaire for smoking in 1995<br>• Data collected on spouse's smoking status<br>• Data collected on exposure to active smoking (see Table 6.15*S*)<br>• Genotype assays for *NAT2*<br>• Subgroups evaluated and stratified by NAT2 acetylator status | • No association with exposure to secondhand smoke from spouse's smoking<br>• No interaction of the *NAT2* genotype with secondhand smoke and risk for breast cancer | **Adulthood:**<br>NA/NP: 1.00<br>Passive only: 1.20 (0.59–2.40) | Controlled for age and menopausal status |

**Table 6.23*S* Continued**

| Study | Design/population | Data collection/ subgroup analyses | Findings for exposure to secondhand smoke | Measures of exposure to secondhand smoke: RR (95% CI) | Confounders |
|---|---|---|---|---|---|
| Sillanpaa et al. 2005a[a] | • Hospital-based study designed to evaluate the main effects for genotypes and modification of other risk factors for breast cancer<br>• 153 nonsmoker cases (invasive) from a total of 483 referred to Kuopio University Hospital<br>• 169 nonsmokers from a total of 482 controls randomly selected from same area as cases using Finnish National Population register<br>• 1990–1995<br>• 37–92 years of age<br>• Finland | • In-person interviews<br>• Data collected for duration of exposure at home and at the workplace<br>• Data collected on exposure to active smoking (see Table 6.15*S*)<br>• Genotype assays for *NAT2*<br>• Subgroups evaluated and stratified by exposure to passive smoke for *NAT2* | • No association between exposure to secondhand smoke and risk for breast cancer<br>• No significant effect modification by *NAT2* genotype<br>• Risk increased in slow *NAT2* phenotype RR = 1.22 (0.75–1.98) | **Adulthood:**<br>NA/NP: 1.00<br>Passive Only: 0.85 (0.62–1.16 | Controlled for age, age at menarche, age at first full-term pregnancy, parity, history of benign breast disease, family history, and alcohol use |

**Table 6.23*S* Continued**

| Study | Design/population | Data collection/ subgroup analyses | Findings for exposure to secondhand smoke | Measures of exposure to secondhand smoke: RR (95% CI) | Confounders |
|---|---|---|---|---|---|
| Lissowska et al. 2006 (Results by menopausal status from Lissowska et al. 2007) | • Population-based study designed to evaluate risk factors for breast cancer<br>• 1,034 incident nonsmoker cases (in situ, invasive) from a total of 2,386 ascertained from five hospitals covering 90% of both cities, supplemented by cancer registry 2000–2003<br>• 1,162 nonsmokers from a total of 2,502 controls randomly selected from the Polish resident database and matched on city and 5-year age groups<br>• 20–74 years of age<br>• Warsaw and Lodz, Poland | • In-person interview<br>• Data collected on exposure at home and/ or at the workplace for at least 1 hour/day for at least 1 year during adulthood<br>• Data collected on exposure to active smoking (see Table 6.15*S*)<br>• Subgroups evaluated by menopausal status and age group (<45, 45–55, and >55 years) | • Nonsignificant association between risk for breast cancer and exposure to passive smoke at home or the workplace<br>• Trend toward increased risk for premenopausal but not postmenopausal women for hours/day-years<br>• No association between risk and exposure by age group | **Adulthood:**<br>NA/NP: 1.00<br>Work or home: 1.10 (0.84–1.45)<br>Home only: 1.08 (0.80–1.46)<br>Work only: 1.36 (0.94–2.00)<br>Home and work: 1.05 (0.77–1.41)<br>**Premenopausal, Hours/Day-Years:**<br>NA/NP: 1.00<br><100: 1.36 (0.67–2.73)<br>101–200: 1.52 (0.73–3.13)<br>>200: 2.02 (0.94–4.36)<br>p trend: 0.08<br>**Postmenopausal, Hours/Day-Years:**<br>NA/NP: 1.00<br><100: 0.96 (0.67–1.39)<br>101–200: 0.90 (0.63–1.30)<br>>200: 1.04 (0.73–1.47)<br>p trend: 0.74 | Controlled for age, site, education, age at menarche, number of full-term births, age at first full-term birth, age at menopause, BMI, family history, prior benign breast biopsy, previous screening mammography, use of oral contraceptives, and HRT |

**Table 6.23*S* Continued**

| Study | Design/population | Data collection/ subgroup analyses | Findings for exposure to secondhand smoke | Measures of exposure to secondhand smoke: RR (95% CI) | Confounders |
|---|---|---|---|---|---|
| Mechanic et al. 2006[a] | • Carolina Breast Cancer Study<br>• Population-based study designed to evaluate causes of breast cancer among African American and White women (Phase I invasive, Phase II in-situ)<br>• 1,211 incident nonsmoker cases (in situ, invasive) from a total of 2,308 ascertained from the North Carolina Cancer Registry for 24 counties in central and eastern North Carolina 1993–2001<br>• 1,087 nonsmokers from a total of 2,022 controls selected from motor vehicle lists (<65 years) and from the Health Care Financing Administration list (≥65 years)<br>• 20–74 years of age<br>• North Carolina | • In-person interviews<br>• Data for exposure to secondhand smoke collected on living with a smoker after 18 years of age<br>• Data collected on exposure to active smoking (see Table 6.15*S*)<br>• Genotypes in *NER* genes<br>• Subgroups evaluated and stratified by ethnicity and *NER* genotype | • Significant association between exposure to passive smoke and risk for breast cancer in African American women only<br>• Nonsignificant trend in risk associated with increasing number of at-risk genotypes in African Americans | **Adulthood, African American:**<br>NA/NP: 1.00<br>Passive only: 1.40 (1.00–1.90)<br>**Adulthood, White:**<br>NA/NP: 1.00<br>Passive only: 1.00 (0.80–1.20) | Controlled for age, age at menarche, age at first full-term pregnancy, parity, family history, and alcohol use |

**Table 6.23*S* Continued**

| Study | Design/population | Data collection/ subgroup analyses | Findings for exposure to secondhand smoke | Measures of exposure to secondhand smoke: RR (95% CI) | Confounders |
|---|---|---|---|---|---|
| Kruk 2007 | • Hospital-based study designed to evaluate association between risk for breast cancer and lifestyle factors by menopausal status<br>• 445 incident nonsmoker cases (invasive) from a total of 858 ascertained from Szczecin Regional Cancer Registry<br>• 730 nonsmokers from a total of 1,085 controls frequency-matched to cases on 5-year age groups and place of residence (urban/rural)<br>• 2003–2007<br>• 28–78 years of age<br>• Western Pomerania region, Poland | • Self-administered questionnaire<br>• Data collected for number of cigarettes/ day by life partner<br>• Data collected on exposure to active smoking (see Table 6.15*S*)<br>• Subgroups evaluated and stratified by menopausal status | • Risk for breast cancer associated with exposure to secondhand smoke regardless of menopausal status<br>• Risk estimate higher for premenopausal women than postmenopausal women<br>• Interaction not significant for menopausal status and exposure to passive smoke (p = 0.77) | **Premenopausal:**<br>Nonsmoker husband: 1.00<br>Smoking husband:<br><20 cig/day: 2.16 (1.49–3.14)<br>≥20 cig/day: 3.79 (2.63–5.47)<br>p trend: <0.0001<br>**Postmenopausal:**<br>Nonsmoker husband: 1.00<br>Smoking husband:<br><20 cig/day: 2.11 (1.56–2.85)<br>≥20 cig/day: 3.15 (2.28–4.35)<br>p trend: <0.0001 | Controlled for age among premenopausal women and age and breast feeding among postmenopausal women |

**Table 6.23*S* Continued**

| Study | Design/population | Data collection/ subgroup analyses | Findings for exposure to secondhand smoke | Measures of exposure to secondhand smoke: RR (95% CI) | Confounders |
|---|---|---|---|---|---|
| Roddam et al. 2007 | • Population-based approach designed to study the association between use of oral contraceptives and risk for breast cancer in premenopausal women<br>• 297 incident nonsmoker cases (invasive) from a total of 639 ascertained through regional and hospital registries<br>• 310 nonsmokers from a total of 640 controls randomly selected from the general practitioners of cases and age-matched<br>• July 1987–February 1990<br>• 36–45 years of age<br>• Thames, Oxford, and Yorkshire regions of the United Kingdom | • In-person interviews<br>• Data collected on living with a smoker for ≥1 year and number of years of exposure<br>• Data collected on exposure to active smoking (see Table 6.15*S*)<br>• Subgroups evaluated and stratified by menopausal status, BMI, family history, and lifestyle factors | • No association between exposure to passive smoke and risk for breast cancer regardless of duration of exposure<br>• No association when results were stratified by menopausal status (only 23 postmenopausal women), use of alcohol, family history, parity, age at birth of first child, SES, BMI, and age at menarche | **Adulthood (Years):**<br>NA/NP: 1.00<br>1–10: 0.99 (0.64–1.53)<br>≥11: 0.84 (0.56–1.25)<br>**Menopausal Status:**<br>NA/NP: 1.00<br>Pre: 0.83 (0.59–1.17)<br>Post: 1.51 (0.19–12.2) | Controlled for SES, alcohol use, BMI, parity, age at birth of first child, use of oral contraceptives, family history, age at menarche, menopausal status, and mutual adjustment for active/passive exposure |

**Table 6.23*S* Continued**

| Study | Design/population | Data collection/ subgroup analyses | Findings for exposure to secondhand smoke | Measures of exposure to secondhand smoke: RR (95% CI) | Confounders |
|---|---|---|---|---|---|
| Rollison et al. 2008 | • Population-based study designed to evaluate detailed exposure data on active smoking and exposure to secondhand smoke at home and the workplace during critical reproductive time periods<br>• 287 total cases; 124 incident nonsmoker cases (invasive) from a total of 287 ascertained through the cancer registry 2000–2002<br>• 116 nonsmokers from a total of 311 controls, frequency-matched by 10-year age groups and selected from motor vehicle driver's license records (<65 years) and from Health Care Financing Administration records for Delaware (≥65 years)<br>• 40–79 years of age<br>• Delaware | • Telephone interviews<br>• Data collected for exposure at home during childhood (<18 years of age ) and adulthood by number of smokers in household, packs/day, hours/day, and during adulthood at the workplace for number of jobs, duration of employment (hours/day), and intensity of exposure (light, moderate, heavy)<br>• Data collected on exposure to active smoking (see Table 6.15*S*) | • No association between risk for breast cancer and exposure to passive smoke during childhood or adulthood | **Lifetime (Both) (Years):**<br>NA/NP: 1.00<br>1–17: 1.30 (0.57–2.98)<br>18–20: 1.04 (0.49–2.25)<br>21–35: 0.79 (0.33–1.87)<br>>36: 1.11 (0.50–2.46)<br>**Adulthood (Home):**<br>NA/NP: 1.00<br>Yes: 1.06 (0.56–2.02)<br>Work:<br>NA/NP: 1.00<br>Any Exposure: 0.80 (0.49–1.32)<br>**Childhood (Years):**<br>NA/NP: 1.00<br>1–8: 0.89 (0.30–2.67)<br>9–17: 0.90 (0.41–1.97)<br>>18: 0.78 (0.43–1.39) | Controlled for age, menopausal status, BMI, age at menarche, age at birth of first child, use of oral contraceptives, family history, and alcohol use |

**Table 6.23*S* Continued**

| Study | Design/population | Data collection/ subgroup analyses | Findings for exposure to secondhand smoke | Measures of exposure to secondhand smoke: RR (95% CI) | Confounders |
|---|---|---|---|---|---|
| Slattery et al. 2008 | • 4-Corners Breast Cancer Study<br>• Population-based study designed to evaluate risk factors for breast cancer among Hispanic, American Indian, and non-Hispanic White women in the southwestern region of the United States<br>• 1,527 total cases; 1,347 incident cases among nonsmokers ascertained through cancer registries (in situ, invasive), premenopausal women (329 Hispanics and American Indians, 535 non-Hispanic Whites), and postmenopausal women (450 Hispanics and American Indians, and 967 non-Hispanic Whites)<br>• 1,601 total controls; 1,442 nonsmokers, frequency matched on ethnicity and 5-year age groups<br>• Women <65 years selected from commercial mailing lists (in Arizona and Colorado) or from driver license lists.<br>• Women ages >65 years selected from Center for Medicare Services list<br>• 1999–2004<br>• 25–79 years of age<br>• Statewide for Utah, New Mexico, and Colorado and 7 counties in Arizona | • In-person interviews.<br>• Data collected for hours/ week in and out of the house during the referent year and at ages 15, 30, and 50 years<br>• Data collected on exposure to active smoking (see Table 6.15*S*)<br>• Genotype assays for 5 IL6 markers and 1 ESR1 marker<br>• Subgroups evaluated and stratified by menopausal status ethnicity, and genotype | • Risk for breast cancer associated with exposure to secondhand smoke for smokers and nonsmokers among pre- and perimenopausal women only<br>• Significant associations limited to Hispanic pre- and perimenopausal women<br>• No association between risk for breast cancer and exposure to secondhand smoke for postmenopausal Hispanic and non-Hispanic White women | **Hours/Week, Premenopausal, Non-Hispanic White:**<br>NA/NP: 1.00<br>1–10: 1.20 (0.70–1.90)<br>>10: 1.20 (0.60–2.70)<br>p trend: 0.44<br>**Hours/Week, Postmenopausal, Non-Hispanic White:**<br>NA/NP: 1.00<br>1–10: 1.00 (0.70–1.50)<br>>10: 1.00 (0.60–1.70)<br>p trend: 0.95<br>**Hours/Week, Premenopausal, Hispanic Women:**<br>NA/NP: 1.00<br>1–10: 0.80 (0.50–1.20)<br>>10: 2.30 (1.20–4.50)<br>p trend: 0.13<br>**Hours/Week, Postmenopausal, Hispanic Women:**<br>NA/NP: 1.00<br>1–10: 1.00 (0.60–1.50)<br>>10: 1.00 (0.60–1.80)<br>p trend = 0.96 | Controlled for age, center, BMI, aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), parity, alcohol use, physical activity, recent (+2 years) estrogen exposure for postmenopausal women, and active smoking (pack-years) |

**Table 6.23*S* Continued**

| Study | Design/population | Data collection/ subgroup analyses | Findings for exposure to secondhand smoke | Measures of exposure to secondhand smoke: RR (95% CI) | Confounders |
|---|---|---|---|---|---|
| Ahern et al. 2009[a] | • Population-based study designed to evaluate the association between risk for breast cancer and lifestyle factors<br>• 557 total cases; 242 incident cases (invasive) among nonsmokers ascertained through the Massachusetts Cancer Registry<br>• 432 total controls; 195 nonsmokers selected randomly from the driver's license bureau (ages <65 years) and from Medicare rosters (ages ≥65 years) in Massachusetts 1989–1991<br>• 28–75 years of age<br>• Massachusetts | • Self-administered, mailed questionnaire<br>• Data collected for ≥2 hours/day of exposure during childhood or adulthood or both<br>• Data collected on exposure to active smoking (see Table 6.15*S*) | • No association between risk for breast cancer and exposure to passive smoke | **Lifetime:**<br>NA/NP: 1.00<br>Passive: 0.97 (0.88–1.08) | Controlled for age at menarche, age at birth of first child, parity, BMI, use of oral contraceptives, hormone replacement therapy, alcohol use, menopausal status, family history, history of benign breast disease, and household income |

**Table 6.23*S* Continued**

| Study | Design/population | Data collection/ subgroup analyses | Findings for exposure to secondhand smoke | Measures of exposure to secondhand smoke: RR (95% CI) | Confounders |
|---|---|---|---|---|---|
| Young et al. 2009 | • Population-based study of secondary analysis to evaluate the association between breast cancer and smoking using combined data from 2 studies with similar target populations, data collection methods, and measures of smoking:<br>• 6,065 total cases; 2,751 incident cases (invasive) among nonsmokers ascertained through the Ontario Cancer Registry<br>• 6,371 total controls; 3,097 nonsmokers frequency matched by 5-year age groups and selected randomly (age-stratified) from the Ontario Ministry of Finance rolls (for OWHS) and from a random-digit dialing list (for OWDHS) OWHS (June 1996–May 1998)<br>• OWDHS (June 2002–April 2003)<br>• Ages 25–75 years<br>• Canada | • Self-administered, mailed questionnaire<br>• Data collected for ≥2 hours/day of exposure during childhood or adulthood or both<br>• Data collected on exposure to active smoking (see Table 6.15S) | • No association between risk for breast cancer and exposure to passive smoke | **Lifetime:**<br>NA/NP: 1.00<br>Passive: 0.97 (0.88–1.08) | Controlled for age at menarche, age at birth of first child, parity, BMI, use of oral contraceptives, hormone replacement therapy, alcohol use, menopausal status, family history, history of benign breast disease, and household income |

*Note:* Data from case-control studies for active cigarette smoking are summarized in Table 6.15*S*. Numbers for cases and controls are based on nonsmokers, a smaller percentage of subjects than the total included for analyses of active cigarette smoking. All results reported by the study may not appear in the summary table.
**BMI** = body mass index; **CI** = confidence interval; **HRT** = hormone replacement therapy; **NA/NP** = no active/no passive; **NSAIDs** = nonsteroidal anti-inflammatory drugs; **OWDHS** = Ontario Women's Diet and Health Study; **OWHS** = Ontario Women's Health Study; **SES** = socioeconomic status.
[a]Overlapping reports based on the same study population.

**Table 6.24S Evaluation of reports on exposure to secondhand smoke among 171 nonsmokers, based on 10 cohort and 24 case-control studies of breast cancer published before 2012 for meta-analyses, by location, study design, analytic sample size, meta-analysis categories, and design or analysis issues (n = 39)**

| | | | Meta-analysis categories | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study** | **Design/population** | **Analytic sample size** | **Premenopausal** | **Postmenopausal** | **Spouse/partner** | **Adult–home** | **Adult–workplace** | **Childhood** | **Adulthood and childhood** | **Adult–any source** | **Ever in lifetime** | **Most comprehensive: Adult–any source vs. ever in lifetime** |
| Millikan et al. 1998[a,b] | • Carolina Breast Cancer Study<br>• Case-control<br>• United States | 274/253 | 1[c] | 1[c] | — | 2 | — | — | — | 1 | — | — |
| Marcus et al. 2000[a,b] | — | 445/423 | — | — | — | — | — | 1[c] | — | — | — | — |
| Mechanic et al. 2006[b] | — | 1,211/1,087 | — | — | 2[c] | 1[c] | — | — | — | 2[c] | — | Adult–any source |
| Reynolds et al. 2004a[a,d] | • California Teachers Study<br>• Cohort<br>• United States | 1,174 of 77,708 | 1[c] | 1[c] | 2[c] | 2[c] | — | 1 | 1[c] | 1 | 1 | — |
| Reynolds et al. 2009[d] | — | 1,754 of 57,523 | 1[c] | 1[c] | — | — | 1[c] | 1[c] | — | 1[c] | 1[c] | Ever in lifetime |
| Metsola et al. 2005[e,f] | • Kuopio Breast Cancer Study<br>• Case control<br>• Finland | 363/351 | — | — | — | — | — | — | — | 1 | — | — |
| Sillanpaa et al. 2005a[f] | — | 363/351 | — | — | — | — | — | — | — | 1[c] | — | Adult–any source |
| Egan et al. 2002[a] | • Nurses Health Study I<br>• Cohort<br>• United States | 1,359 of 35,193 | — | — | — | 1 | — | 1 | — | 1 | — | — |
| Xue et al. 2011[g] | — | 2,890 of 36,017 | — | — | 2[c] | 1[c] | 1[c] | 1[c] | — | 2[c] | 1[c] | Ever in lifetime |
| Sandler et al. 1985a[a,e,h] | • Case-control<br>• North Carolina (hospital) | 32/178 | 1 | 1 | 1 | 2 | — | — | — | 2 | — | Adult–any source |
| Smith et al. 1994[a,e,i] | • National case-control study group<br>• Case-control<br>• United Kingdom | 94/99 | 1 | — | 1 | 1 | 1 | 1 | 1 | 2 | 1 | Ever in lifetime |

**Table 6.24*S* Continued**

| Study | Design/population | Analytic sample size | Meta-analysis categories | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Premenopausal | Postmenopausal | Spouse/partner | Adult–home | Adult–workplace | Childhood | Adulthood and childhood | Adult–any source | Ever in lifetime | Most comprehensive: Adult–any source vs. ever in lifetime |
| Hirose et al. 1995 | • Aichi Cancer Center hospital<br>• Case-control<br>• Nagoya, Japan | 560/1,1276 | 1 | 1 | 1 | 1 | — | — | — | 2 | — | Adult–any source |
| Morabia et al. 1996[a,e,j] | • Case-control<br>• Geneva, Switzerland (hospital) | 126/620 | 1 | — | 1 | 2 | — | — | — | 2 | 1 | Ever in lifetime |
| Jee et al. 1999[a,e,k] | • Korea Medical Insurance Corporation<br>• Cohort<br>• Republic of Korea | 138 of 157,436 | — | — | 1 | 1 | — | — | — | 2 | — | Adult–any source |
| Lash and Ashengrau 1999[a,e] | • Case-control<br>• Cape Cod, Massachusetts | 120/406 | — | 1 | — | — | — | — | — | — | 1 | Ever in lifetime |
| Zhao et al. 1999[a,e] | • Case-control<br>• Chengdu, China (hospital) | 259/252 | — | — | — | — | — | — | — | — | 1 | Ever in lifetime |
| Delfino et al. 2000[a,e] | • Case-control<br>• Orange County, California | 64/147 | 1 | 1 | — | 2 | — | — | — | 1 | — | Adult–any source |
| Johnson et al. 2000[a] | • National Enhanced Cancer Surveillance System<br>• Case-control<br>• Canada | 708/727 | 1 | 1 | — | — | — | 1 | 1 | 1 | 1 | Ever in lifetime |
| Liu et al. 2000[a] | • Case-control<br>• Chongqing, China | 186/186 | — | — | — | 1 | 1 | 1 | — | 2 | — | Adult–any source |
| Nishino et al. 2001[a,e,l] | • Cohort<br>• Miyagi Prefecture, Japan | 67 of 9,675 | — | — | 1 | 2 | — | — | — | 2 | — | Adult–any source |
| Kropp and Chang-Claude 2002[a,m] | • Case-control<br>• Mannheim, Germany | 197/459 | — | — | — | — | — | 1 | 1 | 1 | 1 | Ever in lifetime |
| Lash and Ashengrau 2002[a,e] | • Case-control<br>• Cape Cod, Massachusetts | 305/249 | — | — | — | — | — | — | — | — | 1 | Ever in lifetime |

**Table 6.24*S* Continued**

| Study | Design/population | Analytic sample size | Meta-analysis categories | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Premenopausal | Postmenopausal | Spouse/partner | Adult–home | Adult–workplace | Childhood | Adulthood and childhood | Adult–any source | Ever in lifetime | Most comprehensive: Adult–any source vs. ever in lifetime |
| Alberg et al. 2004[e] | • Campaign Against Cancer and Heart Disease II<br>• Case-control<br>• Washington County, Maryland | 62/66 | — | — | 1 | 1 | — | — | — | 2 | — | Adult–any source |
| Gammon et al. 2004a[a,n] | • Long Island Breast Cancer Study Project<br>• Case-control<br>• United States | 598/627 | 1 | 1 | 1 | 2 | — | 1 | — | 2 | 1 | Ever in lifetime |
| Shrubsole et al. 2004[a,o] | • Shanghai Breast Cancer Study<br>• Case-control<br>• China | 1,013/1,117 | 1 | 1 | 1 | 2 | 1 | — | — | 1 | — | Adult–any source |
| Bonner et al. 2005[a] | • Western New York Exposures and Breast Cancer Study<br>• Case-control<br>• United States | 525/1,010 | 1 | 1 | — | — | 1 | 1 | — | 2 | 1 | Ever in lifetime |
| Gram et al. 2005 | • Norwegian-Swedish Women's Lifestyle and Health Cohort Study<br>• Cohort<br>• Norway and Sweden | 1,130 of 36,773 | — | — | — | — | — | — | — | — | 1 | Ever in lifetime |
| Hanaoka et al. 2005[a,p] | • Japan Public Health Center-based Prospective Study<br>• Cohort<br>• Japan | 162 of 20,169 | 1 | 1 | — | — | 1 | — | — | 2 | 1 | Ever in lifetime |
| Lissowska et al. 2006[q] | • Case control<br>• Warsaw and Lodz, Poland | 1,034/1,162 | 1 | 1 | — | 1 | 1 | — | — | 1 | — | Adult–any source |
| Kruk 2007[e] | • Case control<br>• Western Pomerania region, Poland | 445/730 | 1 | 1 | 1 | 2 | — | — | — | 2 | — | Adult–any source |

**Table 6.24S Continued**

| Study | Design/population | Analytic sample size | Meta-analysis categories | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Premenopausal | Postmenopausal | Spouse/partner | Adult–home | Adult–workplace | Childhood | Adulthood and childhood | Adult–any source | Ever in lifetime | Most comprehensive: Adult–any source vs. ever in lifetime |
| Roddam et al. 2007[r] | • Case-control<br>• Thames, Oxford, and Yorkshire, United Kingdom | 297/310 | 1 | 1 | 1 | 2 | — | — | — | 2 | — | Adult–any source |
| Lin et al. 2008[s] | • Japan Collaborative Cohort Study for Evaluation of Cancer Risk<br>• Cohort<br>• Japan | 140 of 32,023 | — | — | — | 1 | — | 1 | — | 2 | — | Adult–any source |
| Pirie et al. 2008[t] | • Million Women Study<br>• Cohort<br>• United Kingdom | 2,344 of 210,647 | 1 | 1 | 1 | 2 | — | 1 | 1 | 2 | 1 | Ever in lifetime |
| Rollison et al. 2008[u] | • Case-control<br>• Delaware | 124/116 | — | — | — | — | 1 | 1 | — | — | 1 | Ever in lifetime |
| Slattery et al. 2008 | • 4-Corners Breast Cancer Study<br>• Case-control<br>• Arizona, Colorado, New Mexico, and Utah | 1,347/1,442 | 1 | 1 | — | — | — | — | — | — | 1 | Ever in lifetime |
| Ahern et al. 2009[v] | • CBCS<br>• Case-control<br>• Massachusetts | 242/195 | — | — | — | — | — | 1 | 1 | 1 | 2 | Ever in lifetime |
| Young et al. 2009 | • Ontario Women's Health Study<br>• Ontario Women's Diet and Health Study<br>• Case-control<br>• Canada | 2,751/3,097 | — | — | — | — | — | — | — | — | 1 | Ever in lifetime |
| Chuang et al. 2011 | • European Prospective Investigation Into Cancer and Nutrition<br>• Cohort<br>• Europe | 3,187 of 92,956 | — | — | — | — | — | 1 | — | — | 2 | Ever in lifetime |

**Table 6.24*S* Continued**

| Study | Design/population | Analytic sample size | Meta-analysis categories | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Premenopausal | Postmenopausal | Spouse/partner | Adult–home | Adult–workplace | Childhood | Adulthood and childhood | Adult–any source | Ever in lifetime | Most comprehensive: Adult–any source vs. ever in lifetime |
| Luo et al. 2011b[w] | • Women's Health Initiative Observational Study<br>• Cohort<br>• United States | 1,692 of 41,022 | — | 1 | — | 1 | 1 | 1 | 1 | 1 | 1 | Ever in lifetime |
| **Total nonoverlapping reports** | | | **17** | **17** | **15** | **20** | **10** | **15** | **7** | **26** | **20** | **34** |

*Note:* Two studies based entirely on deceased subjects were excluded from all meta-analyses based on exposure to secondhand smoke (Hirayama 1984; Wartenberg et al. 2000). These studies are considered in the section, "Exposure to Tobacco Smoke and Breast Cancer Mortality." Estimates for Adult-any Source and Ever in Lifetime are based on different measures of smoking for those reports providing both measures. Analytic sample size is based on reported number of nonsmokers; for case-control studies, n of cases/n of controls and for cohort studies, n of cases of total count. **1** = estimate directly reported; **2** = estimate inferred (i.e., any adult from spouse). Estimates were abstracted either directly or pooled using other measures of smoking to calculate an estimate for the appropriate category. **USDHHS** = United States Department of Health and Human Services.

[a]Study included in the 2006 Surgeon General's Report (USDHHS 2006).

[b]A series of three reports provide data on the Carolina Breast Cancer Study. Changes were made to the three estimates (Adult–Any Source, Adult–Home, Most Comprehensive) for "All Women" used in the meta-analysis for the 2006 Surgeon General's report. Marcus and colleagues (2000) reported on only exposure to passive smoke during childhood. The study by Mechanic and colleagues (2006), published after the 2006 Surgeon General's Report, was based on a larger number of nonsmokers and provided data on estimates for Adult–Any Source, Adult–Home, Spouse, and Most Comprehensive, which replaced the estimates from Millikan and colleagues (1998), as used in the 2006 Surgeon General's report. However, because Mechanic and colleagues (2006) did not report results by menopausal status, these estimates are based on the initial report (Millikan et al. 1998), which included considerably fewer nonsmokers.

[c]Indicates which report contributes estimates to the meta-analyses when there are overlapping studies.

[d]Two reports provide data on the California Teachers Study. Estimates for Childhood, Adult–Work, Adult–Any Source, Ever in Lifetime, and Most Comprehensive were based on the most recent report (Reynolds et al. 2009). The estimate for Adult–Work exposure was based on any exposure at an age younger than 20 years for 17% of subjects. The estimates for Adult–Spouse, Adult–Home, and both Adulthood and Childhood were based on the earlier report (Reynolds et al. 2004a). The measure for Adult–Home was based on the earlier report because it was specific to exposure at home as an adult, whereas the estimate in the later report included childhood or adulthood exposure at home. Estimates for pre- and postmenopausal status for each exposure measure come from the respective reports. There was no reported estimate for Adult–Work exposure by menopausal status.

[e]Eleven studies excluded after the initial meta-analysis because of design or analysis issues due to inclusion of smokers in passive analyses, inclusion of deceased subjects for whom information was collected from proxies, inclusion of prevalent cases, or small sample size (<100 cases) or insufficient adjustment for relevant covariates (Sandler et al. 1985a; Smith et al. 1994; Morabia et al. 1996; Jee et al. 1999; Lash and Aschengrau 1999, 2002; Zhao et al. 1999; Delfino et al. 2000; Nishino et al. 2001; Alberg et al. 2004; Kruk 2007).

[f]The study reported by Metsola and colleagues (2005) was excluded from all meta-analyses because it was based on the same study population as that reported by Sillanpaa and colleagues (2005a), which adjusted for reproductive factors, use of alcohol, and family history. The latter study was based primarily on postmenopausal women (60%) but did not adjust for menopausal status.

**Table 6.24*S* Continued**

[g]The estimates from Xue and colleagues (2011) for Adult–Work and Adult–Home were pooled across two categories (occasionally and regularly). The estimate for Childhood was pooled across three categories (mother only, father only, and both parents). The estimate for Ever in Lifetime was pooled across four categories based on frequency (occasional/regular), location (home/work), and age (<20 or ≥20 years).
[h]Estimates by menopausal status based on Wells' (1991) reanalysis of data provided by Sandler and colleagues (1985a).
[i]Estimates reported by Smith and colleagues (1994) for all women are also used in the analyses for premenopausal women because all subjects were diagnosed before 36 years of age (Smith et al. 1994). Changes were made to two of the eight estimates extracted from the report by Smith and colleagues (1994) as used in the meta-analysis for the 2006 Surgeon General's report. The estimate for Adult–Any Source was replaced to be the same as that used for Adult–Home, based on the pooled estimates across years of "Adult Exposure from Living with Other Smokers" (RR = 1.33; 95% CI, 0.74–2.40; n = 94 cases, 100 controls), rather than the original "Adult Only, Period of Exposure" (RR = 3.13; 95% CI, 0.73–13.31; n = 21 cases, 27 controls), which increased the sample size and the precision of the RRs and CIs. The estimate for Childhood was replaced with a pooled estimate across two levels of cigarette years under "Total Childhood Exposure" (RR = 1.18; 95% CI, 0.64–2.17; n = 94 cases, 100 controls), rather than the original "Child Only, Period of Exposure" (RR = 1.33; 95% CI, 0.16–10.83; n = 8 cases, 17 controls). These changes were also applied to the premenopausal estimates.
[j]Estimates reported by Morabia and colleagues (1996) appear to be based primarily on postmenopausal women (approximately 70% for cases, 60% for controls), and not adjusted for menopausal status. A single estimate is reported for premenopausal women (RR = 3.6; 95% CI, 1.6–8.2), but the estimate may not have been adjusted for potential confounders; no data are provided. Comments do not address postmenopausal women specifically. The report from Morabia and colleagues (2000) was not included because it presented results from a subsample of the study population previously reported in the earlier study (Morabia et al. 1996).
[k]Changes were made to the estimates for all women extracted from the report by Jee and colleagues (1999) as used in the meta-analysis for the 2006 Surgeon General's report. The category Home was added and based on the pooled estimates used for Spouse (Jee et al. 1999).
[l]Changes were made to three of the four estimates extracted from the report by Nishino and colleagues (2001) as used in the meta-analysis for the 2006 Surgeon General's report. The estimate for Adult–Home was replaced with the pooled estimate for "Husband, and Other Members for Smoking Status in the Household" (RR = 0.69; 95% CI, 0.44–1.06), rather than the original pooled estimate (RR = 0.49; 95% CI, 0.33–0.74), which was based on three estimates that adjusted for only age. Estimates for Adult–Any Source and Most Comprehensive were based on this new estimate. There was no adjustment for menopausal status.
[m]Estimates from Kropp and Chang-Claude (2002) based primarily on premenopausal women (approximately 80%).
[n]Changes were made to the estimates for Spouse, Adult–Home, and Adult–Any Source extracted from Gammon and colleagues (2004a), as used in the meta-analysis for the 2006 Surgeon General's Report. The estimate for Spouse was replaced with the pooled estimate levels for months across "Ever Passively Exposed to Spouse" (n = 260), which was based on Adult-Only Exposure, rather than the set of nonpooled estimates for "Exposed to Passive Smoke Only" (n = 433), based on lifetime exposure as either an adult or as a child in the residence. This resulted in the deletion of menopausal estimates for these three categories because estimates were not associated with pre- and postmenopausal status. An estimate for Ever in Lifetime exposure was added and based on the general category "Exposed to Passive Smoke Only," as noted previously.
[o]Estimates from Shrubsole and colleagues (2004) based on only women who reported being married
[p]Estimates from Hanaoka and colleagues (2005) by menopausal status measured at baseline rather than at diagnosis. Approximately 1% of cases were ascertained through death records.
[q]Estimates originally reported in Lissowska and colleagues (2006) are primarily for postmenopausal women (80%). Estimates for adult exposure by menopausal status were reported in a subsequent publication by Lissowska and colleagues (2007), in response to an editorial by Johnson (2007).
[r]Estimate from Roddam and colleagues (2007) based primarily on premenopausal women (93%).
[s]Estimates from Lin and colleagues (2008) based primarily on postmenopausal women (76%).
[t]Estimates from Pirie and colleagues (2008) based primarily on postmenopausal women (93%). Estimate for passive exposure to tobacco smoke as a child or as an adult were reported by menopausal status and were used for only the Ever in Lifetime and Most Comprehensive categories.
[u]Estimates from Rollison and colleagues (2008) based primarily on postmenopausal women (84%).
[v]Estimates from Ahern and colleagues (2009) for some categories—including estimates for all women by Spouse, Home, and the Workplace and the estimates for menopausal status by Adult–Any Source, Child, and Both—were excluded from the meta-analyses because active smokers were included.
[w]Estimate from Luo and colleagues (2011b) for Childhood and Adulthood was based on pooled estimates across several categories (Childhood and Adult at Home, Childhood and Adult at Work, Childhood and Adult at Home and at Work). All women were postmenopausal.

**Table 6.25*S* Summary of meta-analyses for the broadest categories of exposure to secondhand smoke (adult–any source, ever in lifetime, most comprehensive) for all studies of breast cancer combined and stratified by menopausal status, based on cohort and case-control studies published before 2012**

| | All studies[a] | | | Premenopausal | | | Postmenopausal | | |
|---|---|---|---|---|---|---|---|---|---|
| **Category of exposure to secondhand smoke** | **N** | **RR (95% CI)** | **Q test ($p_h$)** | **N** | **RR (95% CI)** | **Q test ($p_h$)** | **N** | **RR (95% CI)** | **Q test ($p_h$)** |
| **Adult–Any source** | **26** | **1.15 (1.03–1.28)** | **<0.001** | **13** | **1.36 (1.07–1.72)** | **<0.001** | **13** | **1.11 (0.94–1.31)** | **0.001** |
| Cohort studies | 8 | 1.02 (0.92–1.12) | 0.028 | 2 | 1.44 (0.60–3.41) | 0.001 | 3 | 1.01 (0.75–1.36) | 0.044 |
| Case-control studies | 18 | 1.28 (1.07–1.54) | <0.001 | 11 | 1.37 (1.04–1.79) | <0.001 | 10 | 1.16 (0.93–1.45) | 0.001 |
| Exclusion, analysis[b] | 25 | 1.08 (0.99–1.18) | <0.001 | 12 | 1.26 (1.00–1.57) | <0.001 | 12 | 1.04 (0.93–1.16) | 0.208 |
| Exclusion, design[c] | 24 | 1.07 (0.98–1.17) | <0.001 | — | —[d] | — | — | —[d] | — |
| Exclusion, small study bias[e] | 19 | 1.07 (0.98–1.17) | <0.001 | 9 | 1.16 (0.93–1.45) | <0.001 | 10 | 1.04 (0.92–1.18) | 0.111 |
| Exclusion, outlier[f] | 18 | 1.04 (0.96–1.13) | 0.004 | — | —[d] | — | — | —[d] | — |
| *2006 Surgeon General's Report* | *18* | *1.15 (1.02–1.29)* | *<0.001* | *10* | *1.45 (1.04–2.01)* | *<0.001* | *9* | *0.90 (0.81–1.01)* | *0.691* |
| **Ever in lifetime** | **20** | **1.11 (1.03–1.20)** | **<0.001** | **9** | **1.49 (1.14–1.96)** | **0.008** | **9** | **1.05 (0.94–1.17)** | **0.072** |
| Cohort studies | 7 | 1.02 (0.98–1.07) | 0.457 | 3 | 1.23 (0.69–2.19) | 0.027 | 4 | 1.01 (0.85–1.20) | 0.035 |
| Case-control studies | 13 | 1.28 (1.08–1.51) | <0.001 | 6 | 1.64 (1.21–2.23) | 0.077 | 5 | 1.09 (0.92–1.28) | 0.242 |
| Exclusion, analysis[b] | 19 | 1.08 (1.01–1.16) | 0.003 | — | —[d] | — | — | —[d] | — |
| Exclusion, design[c] | 17 | 1.08 (1.01–1.15) | 0.009 | — | —[d] | — | 8 | 1.03 (0.94–1.13) | 0.198 |
| Exclusion, small study bias[e] | 16 | 1.07 (1.00–1.13) | 0.028 | 8 | 1.42 (1.08–1.87) | 0.013 | — | —[d] | — |
| Exclusion, outlier[f] | 15 | 1.03 (0.99–1.07) | 0.389 | 7 | 1.30 (1.02–1.65) | 0.073 | — | —[d] | — |
| *2006 Surgeon General's Report* | *10* | *1.40 (1.12–1.76)* | *<0.001* | *6* | *1.85 (1.19–2.87)* | *0.001* | *5* | *1.04 (0.84–1.30)* | *0.048* |
| **Most comprehensive** | **34** | **1.14 (1.06–1.23)** | **<0.001** | **17** | **1.45 (1.20–1.75)** | **<0.001** | **17** | **1.11 (0.99–1.25)** | **0.001** |
| Cohort studies | 10 | 1.02 (0.95–1.10) | 0.038 | 3 | 1.23 (0.69–2.19) | 0.027 | 4 | 1.01 (0.85–1.20) | 0.035 |
| Case-control studies | 24 | 1.27 (1.11–1.44) | <0.001 | 14 | 1.52 (1.23–1.87) | <0.001 | 13 | 1.18 (1.00–1.39) | 0.004 |
| Exclusion, analysis[b] | 32 | 1.08 (1.01–1.14) | 0.001 | 16 | 1.37 (1.15–1.64) | 0.001 | 16 | 1.05 (0.97–1.14) | 0.182 |
| Exclusion, design[c] | 29 | 1.07 (1.01–1.13) | 0.002 | — | —[d] | — | 15 | 1.04 (0.97–1.11) | 0.361 |
| Exclusion, small study bias[e] | 24 | 1.06 (1.00–1.12) | 0.010 | 13 | 1.27 (1.07–1.49) | 0.010 | 13 | 1.04 (0.96–1.13) | 0.233 |
| Exclusion, outlier[f] | 23 | 1.04 (0.99–1.09) | 0.131 | 12 | 1.21 (1.04–1.40) | 0.063 | — | —[d] | — |
| *2006 Surgeon General's Report* | *21* | *1.20 (1.08–1.35)* | *<.001* | *11* | *1.64 (1.25–2.14)* | *0.001* | *10* | *1.00 (0.88–1.12)* | *0.321* |

*Note:* Estimates were abstracted either directly or pooled using other measures of smoking to calculate an estimate for the appropriate category. Cochran's $\chi 2$ test, reported as the Q-test statistic, was used to assess between-study heterogeneity ($p_h$); $p_h$ values reported in SAS as 0.000 due to rounding shown in table as <0.001. Table 6.24*S* provides more details about which studies contributed to exposure categories and reasons for exclusions. Summary estimates for all meta-analyses are based on random-effects models. **CI** = confidence interval; **N** = sample size (number of studies); **RR** = relative risk.

**Table 6.25*S* Continued**

[a]All studies regardless of whether the majority of subjects were primarily premenopausal or postmenopausal. This includes those studies that had a small percentage (<20%) of either pre- or postmenopausal women (Kropp and Chang-Claude 2002; Sillanpaa et al. 2005a; Roddam et al. 2007; Pirie et al. 2008; Rollison et al. 2008; Lin et al. 2008), no premenopausal women (Luo et al. 2011b) or no postmenopausal women (Smith et al. 1994). Because some studies did not stratify results by menopause, the numbers of pre- and postmenopausal studies do not always sum to equal All Studies.
[b]Excludes two studies (Zhao et al. 1999; Kruk 2007) from the appropriate categories (Table 6.24*S*).
[c]Excludes two studies (*note b*) and three studies (Jee et al. 1999; Lash and Aschengrau 1999; Lash and Aschengrau 2002) from the appropriate categories (Table 6.24*S*).
[d]Indicates that the estimate did not change because studies were excluded based on previous sensitivity analyses or did not include an estimate for the specific measure of smoking by menopausal status.
[e]Excludes five studies (*notes b and c*) and five studies (Sandler et al. 1985a; Smith et al. 1994; Delfino et al. 2000; Nishino et al. 2001; Alberg et al. 2004) from the appropriate categories (Table 6.24*S*).
[f]Excludes 10 studies (*notes b, c, and e*) and 1 study (Morabia et al. 1996) (Table 6.24*S*, *note e*), an extreme outlier from All Studies for all three measures of smoking and from premenopausal estimates for Ever in Lifetime and Most Comprehensive. See Figure 6.43.

**Table 6.26*S* Summary of meta-analyses for specific categories of exposure to secondhand smoke (spouse, home, workplace, childhood, childhood and adulthood) for all studies of breast cancer combined and stratified by menopausal status, based on cohort and case-control studies published before 2012**

| | All studies[a] | | | Premenopausal | | | Postmenopausal | | |
|---|---|---|---|---|---|---|---|---|---|
| **Category of exposure to secondhand smoke** | **N** | **RR (95% CI)** | **Q test ($p_h$)** | **N** | **RR (95% CI)** | **Q test ($p_h$)** | **N** | **RR (95% CI)** | **Q test ($p_h$)** |
| **Adulthood** | | | | | | | | | |
| Spouse | 15 | 1.22 (1.05–1.42) | <0.001 | 7 | 1.32 (0.97–1.80) | 0.002 | 6 | 1.19 (0.78–1.82) | <0.001 |
| Cohort studies | 5 | 1.02 (0.93–1.13) | 0.151 | 1 | 1.01 (0.66–1.54) | — | 1 | 0.88 (0.71–1.09) | — |
| Case-control studies | 10 | 1.43 (1.09–1.87) | <0.001 | 6 | 1.41 (0.98–2.04) | 0.001 | 5 | 1.30 (0.77–2.17) | 0.002 |
| Exclusions[b] | 8 | 1.05 (0.97–1.13) | 0.185 | 4 | 1.05 (0.89–1.22) | 0.479 | 4 | 1.00 (0.70–1.40) | 0.037 |
| *2006 Surgeon General's Report* | *9* | *1.17 (0.96–1.44)* | *0.002* | *4* | *1.40 (0.92–2.12)* | *0.100* | *3* | *0.86 (0.67–1.12)* | *0.645* |
| Home | 20 | 1.16 (1.02–1.31) | <0.001 | 9 | 1.35 (1.03–1.78) | 0.003 | 9 | 1.13 (0.85–1.50) | <0.001 |
| Cohort studies | 7 | 0.97 (0.87–1.08) | 0.031 | 1 | 1.01 (0.66–1.54) | — | 2 | 0.89 (0.76–1.05) | 0.846 |
| Case-control studies | 13 | 1.38 (1.11–1.71) | <0.001 | 8 | 1.44 (1.05–1.97) | 0.002 | 7 | 1.25 (0.86–1.83) | 0.006 |
| Exclusions[c] | 12 | 1.02 (0.94–1.11) | 0.061 | 5 | 1.07 (0.92–1.24) | 0.450 | 6 | 1.00 (0.81–1.23) | 0.097 |
| *2006 Surgeon General's Report* | *8* | *1.01 (0.85–1.19)* | *0.006* | *4* | *1.28 (0.94–1.74)* | *0.355* | *3* | *0.92 (0.76–1.11)* | *0.591* |
| Workplace | 10 | 1.03 (0.92–1.15) | 0.034 | 4 | 1.21 (0.70–2.09) | <0.001 | 4 | 0.92 (0.72–1.16) | 0.120 |
| Cohort studies | 4 | 1.00 (0.92–1.08) | 0.349 | 1 | 2.30 (1.40–3.79) | — | 2 | 0.69 (0.28–1.69) | 0.029 |
| Case-control studies | 6 | 1.10 (0.85–1.43) | 0.011 | 3 | 0.98 (0.60–1.58) | 0.014 | 2 | 0.92 (0.75–1.13) | 0.311 |
| Exclusions[d] | 9 | 1.02 (0.91–1.13) | 0.039 | 3 | 1.15 (0.59–2.24) | <0.001 | — | —[e] | — |
| *2006 Surgeon General's Report* | *6* | *1.06 (0.84–1.35)* | *0.008* | *4* | *1.21 (0.70–2.19)* | *<0.001* | *3* | *0.83 (0.53–1.29)* | *0.086* |
| **Childhood** | **15** | **1.01 (0.95–1.07)** | **0.199** | **4** | **1.12 (0.90–1.40)** | **0.262** | **4** | **1.15 (1.03–1.28)** | **0.888** |
| Cohort studies | 6 | 1.00 (0.95–1.05) | 0.349 | 1 | 0.95 (0.77–1.18) | — | 2 | 1.14 (1.00–1.30) | 0.683 |
| Case-control studies | 9 | 1.01 (0.88–1.17) | 0.138 | 3 | 1.34 (1.02–1.75) | 0.862 | 2 | 1.17 (0.95–1.43) | 0.513 |
| Exclusions[d] | 14 | 1.01 (0.95–1.07) | 0.160 | 3 | 1.14 (0.84–1.54) | 0.141 | — | —[e] | — |
| *2006 Surgeon General's Report* | *9* | *1.01 (0.90–1.12)* | *0.101* | *4* | *1.14 (0.90–1.45)* | *0.342* | *3* | *1.04 (0.86–1.26)* | *0.242* |
| **Childhood and Adulthood** | **7** | **1.09 (0.95–1.24)** | **0.102** | **3** | **1.63 (0.68–3.91)** | **0.016** | **3** | **1.05 (0.89–1.24)** | **0.162** |
| Cohort studies | 3 | 1.03 (0.94–1.14) | 0.234 | 1 | 0.87 (0.60–1.26) | — | 2 | 1.02 (0.84–1.23) | 0.092 |
| Case-control studies | 4 | 1.49 (1.10–2.04) | 0.439 | 2 | 2.61 (1.36–5.02) | 0.988 | 1 | 1.30 (0.82–2.06) | — |
| Exclusions[d] | 6 | 1.07 (0.95–1.21) | 0.124 | 2 | 1.43 (0.49–4.15) | 0.011 | — | —[e] | — |
| *2006 Surgeon General's Report* | *4* | *1.39 (0.88–2.18)* | *0.021* | *3* | *1.63 (0.68–3.91)* | *0.016* | *2* | *1.02 (0.74–1.42)* | *0.160* |

*Note:* Estimates were abstracted either directly or pooled using other measures of smoking to calculate an estimate for the appropriate category. Cochran's $\chi 2$ test, reported as the Q-test statistic, was used to assess between-study heterogeneity ($p_h$). Table 6.24*S* provides more details about which studies contributed to exposure categories and reasons for exclusions. Summary estimates for all meta-analyses are based on random-effects models. **CI** = confidence interval; **N** = sample size (number of studies);

**Table 6.26*S* Continued**

**RR** = relative risk.

[a]All studies regardless of whether the majority of subjects were primarily premenopausal or postmenopausal. This includes those studies that had a small percentage (<20%) of either pre- or postmenopausal women (Kropp and Chang-Claude 2002; Sillanpaa et al. 2005a; Roddam et al. 2007; Pirie et al. 2008; Rollison et al. 2008; Lin et al. 2008), no premenopausal women (Luo et al. 2011b) or no postmenopausal women (Smith et al. 1994). Because some studies did not stratify results by menopause, the numbers of pre- and postmenopausal studies do not always sum to equal All Studies.

[b]Excludes seven studies from All Studies: (Sandler et al. 1985a; Smith et al. 1994; Morabia et al. 1996; Jee et al. 1999; Nishino et al. 2001; Alberg et al. 2004; Kruk 2007); three studies from Premenopausal: (Sandler et al. 1985a; Smith et al. 1994; Kruk 2007); and two studies from Postmenopausal (Sandler et al. 1985a; Kruk 2007).

[c]Excludes seven studies (*note b)* in addition to one more (Delfino et al. 2000) from All Studies and from Premenopausal due to small sample size and insufficient adjustment for relevant covariates.

[d]Excludes one study (Smith et al. 1994) from All Studies and from Premenopausal due to small sample size and insufficient adjustment for relevant covariates.

[e]Indicates that the estimate did not change because studies were excluded based on previous sensitivity analyses or did not include an estimate for the specific measure of smoking by menopausal status.

**Table 6.27*S* Comparison of relative risks (RRs) from selected summaries of meta-analyses for active smoking *versus* exposure to secondhand smoke for all studies of breast cancer combined and stratified by study design**

| Measures of smoking | N | All studies: RR (95% CI) | N | Cohort studies: RR (95% CI) | N | Case-control studies: RR (95% CI) |
|---|---|---|---|---|---|---|
| **Active smoking** | | | | | | |
| Ever smoker[a] | 46 | 1.12 (1.07–1.17)<br>1.10 (1.07–1.12) | 19 | 1.10 (1.07–1.13)<br>1.10 (1.07–1.13) | 27 | 1.15 (1.06–1.25)<br>1.11 (1.07–1.15) |
| Ever smoker, most restricted[b] | 30 | 1.09 (1.06–1.12)<br>1.09 (1.06–1.12) | 11 | 1.10 (1.07–1.13)<br>1.10 (1.07–1.13) | 19 | 1.08 (1.03–1.13)<br>1.07 (1.03–1.12)<br>1.10 (1.07–1.12) |
| No active-only[b] | 25 | 1.09 (1.06–1.13)<br>1.09 (1.06–1.12) | 11 | 1.10 (1.07–1.14)<br>1.10 (1.06–1.14) | 14 | 1.08 (1.02–1.15)<br>1.06 (1.02–1.11) |
| Current smoker[b] | 25 | 1.12 (1.08-1.16)<br>1.12 (1.08-1.16) | 11 | 1.14 (1.10–1.18)<br>1.14 (1.10-1.18) | 14 | 1.07 (1.00–1.16)<br>1.07 (1.00–1.14) |
| Former smoker[b] | 25 | 1.09 (1.05–1.13)<br>1.08 (1.05–1.10) | 11 | 1.09 (1.03–1.14)<br>1.07 (1.04–1.10) | 14 | 1.09 (1.03–1.16)<br>1.09 (1.03–1.15) |
| Duration of smoking, ≥20 years[b] | 19 | 1.16 (1.12–1.21)<br>1.16 (1.12–1.20) | 7 | 1.15 (1.10–1.19)<br>1.15 (1.10–1.19) | 12 | 1.23 (1.12–1.36)<br>1.21 (1.12–1.30) |
| Cigarettes/day, ≥20[b] | 18 | 1.13 (1.09–1.17)<br>1.13 (1.09–1.17) | 8 | 1.12 (1.08–1.17)<br>1.12 (1.08–1.17) | 10 | 1.19 (1.06–1.33)<br>1.19 (1.06–1.33) |
| Pack-years, ≥20[b] | 16 | 1.16 (1.11–1.21)<br>1.15 (1.11–1.19) | 6 | 1.15 (1.10–1.19)<br>1.14 (1.10–1.19) | 10 | 1.21 (1.09–1.34)<br>1.21 (1.10–1.33) |
| **Exposure to secondhand smoke** | | | | | | |
| Most comprehensive[a] | 34 | 1.14 (1.06–1.23)<br>1.06 (1.02–1.09) | 10 | 1.02 (0.95–1.10)<br>1.02 (.97–1.06) | 24 | 1.27 (1.12–1.44)<br>1.13 (1.07–1.19) |
| Most comprehensive, most restricted[b] | 23 | 1.04 (0.99–1.09)<br>1.03 (.99–1.06) | 8 | 1.02 (0.96–1.09)<br>1.01 (.97–1.06) | 15 | 1.07 (1.00–1.14)<br>1.05 (.99–1.12) |
| Adult–Any source, most restricted[b] | 18 | 1.04 (0.96–1.13)<br>1.01 (.97–1.06) | 6 | 1.01 (0.93–1.11)<br>1.00 (.96–1.05) | 12 | 1.08 (0.94–1.24)<br>1.05 (.96–1.13) |
| Ever in Lifetime, most restricted[b] | 15 | 1.03 (0.99–1.07)<br>1.03 (.99–1.07) | 7 | 1.02 (0.98–1.07)<br>1.02 (.98–1.07) | 8 | 1.07 (0.97–1.18)<br>1.04 (.97–1.12) |
| Lifelong, Childhood & Adulthood, most restricted[b] | 6 | 1.07 (0.95–1.21)<br>1.06 (.98–1.14) | 3 | 1.03 (0.94–1.14)<br>1.04 (.96–1.12) | 3 | 1.44 (1.05–1.99)<br>1.44 (1.05–1.99) |

*Note:* **CI** = confidence interval; **N** = sample size (number of studies). Sumary estimates for meta-analyses based on random effects models with exception of fixed-effects estimates shown in italics.

[a]Based on total studies.

[b]Restricted set of studies based on criteria notes to Tables 6.16*S*–6.17*S* and 6.24*S*–6.26*S*.

**Table 6.28*S* Associations between smoking and overall mortality in cancer patients**

| Study | Design/population | Smoking definition | Findings (all comparisons are vs. never unless otherwise specified) | Comments |
|---|---|---|---|---|
| Goodman et al. 1990 | • 675 lung cancer patients | C/F/N | • Males:<br>– Never: 1.0<br>– Former: 1.0 (0.6–1.5)<br>– Current: 0.8 (0.5–1.3)<br>• Females:<br>– Never: 1.0<br>– Former: 1.6 (1.0–2.4)<br>– Current: 1.5 (0.9–2.4) | 1979-1985; detailed interview |
| Sobue et al. 1991 | • 267 lung adenocarcinoma patients | C/F/N | • Former: 1.89 (0.88–4.04)<br>• Current:<br>– <50 Pack-years: 1.28 (0.68–2.40)<br>– 50+ Pack-years: 2.38 (1.21–4.67) | 1978–1987 |
| Browman et al. 1993 | • 115 Stage III–IV head/neck cancer patients | Current/noncurrent | • 2.3 (1.2–4.2) | Smoking during RT; patients treated with RT +/- chemotherapy |
| Kirschner et al. 1995 | • 136 vulvar cancer patients | Smoker/ Nonsmoker | • 6.34 (p <0.01) | Smoking not clearly defined; chart review |
| Deleyiannis et al. 1996 | • 649 head/neck cancer patients | C/F/N | • Current ≥ 20 cpd 1.0 (referent)<br>• Current <20 cpd 0.68 (0.38–1.24)<br>• Quit <15 yrs ago 0.99 (0.54–1.80)<br>• Never/quit ≥15yrs: 0.42 (0.24–0.74) | 1983–1987; structured interview; referent category = current smokers with ≥20 cpd |
| Boffetta et al. 1997 | • 222 male laryngeal cancer patients | Cigarettes per day | • 0–15 cpd 1.0 (referent)<br>• 16–25: 1.4 (0.9–2.2)<br>• ≥26: 1.8 (1.1–2.9) | 1979–1982; chart review |
| Yu et al. 1997 | • 25,436 cancer patients from institutional tumor registry. | Ever/never | • 1.47 (1.4–1.6) | |
| Fujusawa et al. 1999 | • 369 Stage I NSCLC patients | Pack-years | • <30: 1.0 (referent)<br>• 30+: 2.41 (1.24–4.96) | 1981–1993; patients treated with surgery |
| de Perrot et al. 2000 | • 1046 Stage I–IV NSCLC patients | Pack-years | • 0: 1.0 (referent)<br>• 1-40: 1.82 (1.22–2.72)<br>• >40: 1.48 (0.99–2.21) | 1977–1996; chart review, patients treated with surgery |
| Hommura et al. 2000 | • 215 Stage I–IV NSCLC patients | Ever/Never | • 1.73 (0.80–3.73) | 1976–1994; chart review; smoking not clearly defined |
| Huang et al. 2000 | • 877 gastric cancer patients | C/F/N | • Ever: 2.10 (1.06–4.18)<br>• Current: 2.54 (1.22–5.29) | 1988–1994; only male results, no analyses performed for women. |

**Table 6.28*S* Continued**

| Study | Design/population | Smoking definition | Findings (all comparisons are vs. never unless otherwise specified) | Comments |
|---|---|---|---|---|
| Palli et al. 2000 | • 382 gastric cancer patients | C/F/N | • Former: 1.07 (0.78–1.47)<br>• Current: 1.04 (0.75–1.45) | 1985–1987; structured questionnaire in year prior to surgery |
| Sweeney et al. 2000 | • 555 renal cell cancer patients | C/F/N | • Former: 1.2 (0.8–1.7)<br>• Current: 1.7 (1.2–2.5) | 1995–1997; chart review |
| Lippman and Farrow 2001 | • 1166 T1–3 NSCLC patients | C/F/N | • Former: 2.28 (0.58–8.92)<br>• Current: 4.39 (1.11–17.29) | Randomized trial; patients treated with isoretinoin |
| Browman et al. 2002 | • 148 Stage III–IV head/neck cancer patients | Current/noncurrent | • 1.17 (p = 0.07) | Comparison group is recent quitters who stopped smoking within 12 weeks prior to RT; patients treated with RT |
| Chiyo et al. 2003 | • 931 lung cancer patients | Ever/Never | • 1.51 (1.14–2.08) | 1980–1990; chart review; smoking not clearly defined (smoking history) |
| de Cassia Braga Ribeiro et al. 2003 | • 530 head/neck cancer patients | Smoker/nonsmoker | • 1.5 (p = 0.03) | 1990–1997; smoking not clearly defined; chart review; patients treated with curative surgery |
| Myrdal et al. 2003 | • 395 Stage I–III NSCLC patients | Current, non-current | • 1.3 (1.1–1.6) | 1987–1999; chart review; patients treated with surgery |
| Tan et al. 2003 | • 326 women with Stage I NSCLC | Ever, never | • 1.3 (1.0–1.8) | 1996–1998 |
| Videtic et al. 2003 | • 186 limited stage SCLC patients | Current, non-current | • 1.86 (1.34–2.57) | 1989–1999; chart review, patients treated with chemoradiotherapy |
| Chang et al. 2004b | • 114 CML patients | Ever/Never | • 1.72 (0.86–3.46) | 1997–2001; patients treated with hematopoietic stem cell transplant. 1-year mortality |
| Nordquist et al. 2004 | • 654 Stage I–IV NSCLC patients | Current, Never | • 1.33 (1.04–1.69) | (1985–2000, Moffitt) |
| Pickles et al. 2004 | • 601 prostate cancer patients | Current/ Noncurrent | • 2.38 (p = 0.009) | 1994–1997; 6 year mortality; patients treated with external beam RT; reference category includes never and former smokers |
| Sawabata et al. 2004 | • 242 Stage IA NSCLC patients | Smoker | • Preoperative smoking yes: 5.706, p=0.1 | 1991–2003; patients treated with surgery; chart review; smoking not clearly defined |

**Table 6.28*S* Continued**

| Study | Design/population | Smoking definition | Findings (all comparisons are vs. never unless otherwise specified) | Comments |
|---|---|---|---|---|
| Tammemagi et al. 2004 | • 1,155 lung cancer patients | Current, non-current | • 1.26 (1.08–1.47) | 1995–1998; chart review |
| Toh et al. 2004 | • 317 Stage I–IV NSCLC patients | Ever/Never | • 0.98 (0.704–1.375) | 1999–2002; chart review |
| Dikshit et al. 2005a | • 931 laryngeal or hypopharyngeal cancer patients | Current cpd | • 1–15 cpd: 1.8 (1.1–3.1)<br>• 16–25 cpd: 1.7 (1.0–2.9)<br>• >25 cpd: 1.8 (1.1–3.1) | 1979–1982 |
| Ebbert et al. 2005 | • 5229 lung cancer patients | C/F/N | • NSCLC<br>– Former: 0.99 (0.86–1.13)<br>– Current: 1.15 (1.00–1.32)<br>• SCLC<br>– Former: 1.05 (0.57–1.94)<br>– Current: 1.08 (0.58–1.99) | 1997–2002 |
| Kawai et al. 2005 | • 3082 Stage IA NSCLC patients | Pack-years | • <40 Pack-years: 1.0<br>• 40+ Pack-years: 1.129 (0.948–1.344) | 1982–1997; chart review; patients treated with surgery |
| Sardari et al. 2005 | • 321 Stage I–IIIB NSCLC patients | C/F/N | • Current: 1.0<br>• Recent quitters: 0.34 (0.16–0.71)<br>• Former: 0.54 (0.35–0.84)<br>• Never: 0.45 (0.21–0.97) | 1991–2001; patients treated with surgery; detailed smoking information; recent quit within 3 months |
| Trivers et al. 2005 | • 1,142 esophageal and gastric cancer patients | Ever/Never | • Esophageal adenocarcinoma<br>– 0.86 (0.64–1.16)<br>• Gastric cardia adenocarcinoma<br>– 0.99 (0.71–1.38)<br>• Esophageal squamous cell carcinoma<br>– 0.99 (0.62–1.59)<br>• Other gastric adenocarcinomas<br>– 1.02 (0.79–1.32) | 1993–1995 |
| Wright et al. 2005 | • 255 IB-IIB cervical cancer patients | Current/Noncurrent | • 3.69 (1.08–12.62) | Reference category includes former and never smokers |
| Wu et al. 2005 | • 301 Stage I–III NSCLC patients | Smoker | • Stage I–III: 1.40 (0.997–1.97)<br>• Stage II-III: 1.76 (1.17–2.66) | 1990–2001; smoking not clearly defined in analysis; patients treated with surgery |
| Ando et al. 2006 | • 1,976 NSCLC patients | Ever/Never | • 1.41 (1.19–1.67) | 2002; chart review; patients from 84 institutions treated with gefitinib |

**Table 6.28*S* Continued**

| Study | Design/population | Smoking definition | Findings (all comparisons are vs. never unless otherwise specified) | Comments |
|---|---|---|---|---|
| Battaglioli et al. 2006 | • 1,138 NHL patients | C/F/N | • Former: 0.91 (0.73–1.14)<br>• Current: 1.04 (0.84–1.29) | 1991–1993; structured questionnaire after diagnosis |
| Heist et al. 2006 | • 382 Stage I NSCLC patients | C/F/N, Pack-years | • Former: 1.39 (0.74–2.59)<br>• Current: 1.61 (0.86–3.03)<br>• Pack-years: 1.007 (1.003–1.01) | 1992–2001; patients treated with surgery |
| Iyoda et al. 2006 | • 335 Stage IA NSCLC patients | Index | • 0: 1.0 (referent)<br>• 1+: 1.24 (0.53–2.92) | 1988–2003; chart review; smoking not clearly defined in analysis |
| Khuri et al. 2006 | • 1,190 Stage I–II head/neck cancer patients | C/F/N | • Current vs. former: 1.60 (1.23–2.07)<br>• Current vs. never: 2.51 (1.54–4.10) | Patients treated with surgery +/- RT and on randomized phase III trial of isotretinoin vs. placebo |
| Merrick et al. 2006 | • 938 consecutive T1b-T3a prostate cancer patients | C/F/N | • Former: 2.15 (p = 0.007)<br>• Current: 4.27 (p <0.001) | 1995–2002; patients treated with brachytherapy +/- androgen deprivation therapy |
| Modesitt et al. 2006 | • 3,562 endometrial cancer patients | Current/Notcurrent | • 1.41 (1.20–1.66) | 1995–2002; reference category includes never and former smokers |
| Mulligan et al. 2006 | • 907 NSCLC patients | Pack-years | • <40: 1.0 (referent)<br>• 40-60: 1.11 (0.79–1.56)<br>• >60: 1.00 (0.72–1.39)<br>• Duration of smoking cessation<br>– 0 years: 1.00 (referent)<br>– 0–7 years: 1.17 (0.82–1.67)<br>– 7–15 years: 0.70 (0.49–0.99)<br>– >15 years: 1.03 (0.71–1.50) | 1980–2000. Walter Reed Army Medical Center Tumor Registry; referent group includes smokers with <40 Pack-years |
| Saito-Nakaya et al. 2006 | • 238 Stage I–IIIA NSCLC patients | C/F/N | • Smoking at 1 month after surgery<br>– Never: 1.0 (referent)<br>– Former: 3.4 (1.5–7.6)<br>• Quit in past year: 2.9 (1.4–6.3)<br>• Current: 6.4 (1.7–23.9) | 1996–1999 |
| Sun et al. 2006 | • 5,730 Stage I–IV NSCLC patients | C/F/N | • Former: 1.13 (1.00–1.28)<br>• Current: 1.09 (0.97–1.23) | 1997–2003; chart review |
| Tsao et al. 2006 | • 1370 Stage III–IV patients | C/F/N | • Never: 1.0 (referent)<br>• Former: 1.47 (p=0.003)<br>• Current: 1.55 (p=0.0004) | 1993–2002; patients received chemotherapy; chart review |

**Table 6.28*S* Continued**

| Study | Design/population | Smoking definition | Findings (all comparisons are vs. never unless otherwise specified) | Comments |
|---|---|---|---|---|
| Waggoner et al. 2006 | • 315 advanced cervical cancer patients | Current/ Noncurrent | • 1.51 (1.01–2.27) | Data from GOG 165 trial; reference category includes former and never smokers |
| Yoshino et al. 2006 | • 999 Stage I–IV NSCLC patients | Smoker | • Stage I: 1.73 (1.01–3.04)<br>• Stage II: NS (p=0.90)<br>• Stage III–IV: NS (p=0.61) | Chart review; smoking defined as smoking within 10 years of diagnosis |
| Zhou et al. 2006 | • 543 Stage I–IIB NSCLC patients | C/F/N | • Current: 1.0 (referent)<br>• Former:<br>– Quit 1-8 yr: 0.82 (0.59–1.13)<br>– Quit 9-17 yr: 0.69 (0.49–0.97)<br>– Quit 18+ yr: 0.66 (0.45–0.95)<br>• Never: 0.54 (0.29–1.00) | 1992–2002; current smoking is referent group |
| Ademuyiwa et al. 2007 | • 208 Stage III NSCLC patients | Current/Non-current | • 0.90 (0.55–1.44) | 2002–2006; patients treated with chemoradiotherapy +/- adjuvant chemotherapy on Hoosier Oncology Group Study |
| Bryant et al. 2007 | • 730 Stage I–IV NSCLC patients | Ever/Never | • 1.21 (0.98–1.39) | 1999–2005 |
| Chia et al. 2007 | • 745 endometrial cancer patients | C/F/N | • Former: 1.2 (0.8–1.8)<br>• Current: 1.2 (0.7–2.1) | 1991–1994; structured health behavior assessment |
| Holmes et al. 2007 | • 5,056 breast cancer patients | C/F/N | • Former: 1.04 (0.90–1.19)<br>• Current: 1.43 (1.24–1.65) | Nurses' Health Study; repeated structured questionnaires |
| Hung JJ et al. 2007 | • 445 Stage I NSCLC patients with tumors 3 cm or less | Pack-years | • 1.01 (1.01–1.02) | 1980–2000; chart review; pack-years analyzed as continuous variable |
| Kato et al. 2007 | • 267 Stage I–IIIA NSCLC patients | Ever/Never | • 1.88 (1.09–3.24) | Smoking not clearly defined in analysis |
| Kikuchi et al. 2007 | • 161 Stage I–IV NSCLC patients | Ever/Never | • 2.04 (0.99–4.64) | 1982–1994; chart review; patients treated with surgery |
| Pantarotto et al. 2007 | • 416 prostate cancer patients | C/F/N | • Former: 1.51 (p = 0.11)<br>• Current: 1.72 (p = 0.08) | 1990–1999; patients treated with external beam RT; chart review |

**Table 6.28*S* Continued**

| Study | Design/population | Smoking definition | Findings (all comparisons are vs. never unless otherwise specified) | Comments |
|---|---|---|---|---|
| Sagiv et al. 2007 | • 1,273 breast cancer patients | C/F/N | • Obese<br>– Former: 1.70 (0.94–3.07)<br>– Current: 2.10 (1.03–4.27)<br>• Overweight<br>– Former: 0.92 (0.51–1.67)<br>– Current: 1.10 (0.52–2.35)<br>• Normal weight<br>– Former: 1.08 (0.62–1.87)<br>– Current: 1.00 (0.54–1.86) | 1996–1997; Long Island Breast Cancer Study Project; questionnaire following breast cancer diagnosis |
| Samadi et al. 2007 | • 420 esophageal or gastric cancer patients | Smoker/Nonsmoker | • 1.81 (1.02–3.23) | 1994–2005; smoking not clearly defined in analysis |
| Wang et al. 2007 | • 426 Stage I NSCLC patients | Ever/Never | • 1.11 (0.77–1.58) | 1995–2000; chart review; smoking not clearly defined; patients treated with surgery |
| Arduino et al. 2008 | • 334 oral cavity cancer patients, | Smoker/nonsmoker | • 1.3 (p = 0.15) | 10-year mortality; chart review |
| Dal Maso et al. 2008 | • 1,453 breast cancer patients | C/F/N | • Former: .41 (1.11–1.78)<br>– Current <15 cpd: 1.48 (1.12–1.94)<br>– Current ≥15 cpd: 1.35 (0.94–1.93) | 1991–1994; structured questionnaire 1 year prior to diagnosis |
| Hanagiri et al. 2008 | • 770 stage I–IV NSCLC patients | Ever/Never | • 1.03 (0.76–1.45) | 1994–1995; chart review; patients treated with surgery |
| Karvonen-Gutierrez et al. 2008 | • 495 head/neck cancer patients | Smoke/No smoke past month | • 1.72 (1.29–2.29) | 2000–2002; structured health habits assessment |
| Matsuguma et al. 2008 | • 455 state I NSCLC patients | Ever/Never | • 1.27 (0.72–2.24) | 1986–2003; chart review; patients treated with surgery |
| Meyer et al. 2008 | • 540 head/neck cancer patients | Current/noncurrent | • 2.26 (1.29–3.97) (β-carotene treated pts.) | 1994–2000; patients treated with RT, randomized to β-carotene; reference category includes never and former smokers |
| Molina et al. 2008 | • 20,915 head/neck cancer patients | Ever/Never | • 1.34 (1.19–1.50) | 1998–2002; Florida Cancer Data System |
| Nakamura et al. 2008 | • 571 lung cancer patients | C/F/N | • Former: 1.70 (1.25–1.31)<br>• Current: 1.99 (1.51–2.62) | 1980–2003 |

**Table 6.28*S* Continued**

| Study | Design/population | Smoking definition | Findings (all comparisons are vs. never unless otherwise specified) | Comments |
|---|---|---|---|---|
| Ramamoorthy et al. 2008 | • 64 anal cancer patients | Smoker/Nonsmoker | • 2.25 (p=0.05) | 1999–2005; smoking within 5 years of treatment; 5-year mortality; chart review |
| Saito-Nakaya et al. 2008 | • 1,230 Stage I–IV NSCLC patients | C/F/N | • Males<br>– Former: 1.6 (0.9–2.6)<br>– Current: 1.7 (1.1–2.8)<br>• Females<br>– Former: 1.1 (0.7–1.9)<br>– Current: 2.0 (1.4–2.9) | 1999–2004 |
| Sundelof et al. 2008 | • 580 esophageal or gastric cardia cancer patients | C/F/N | • Oesophageal adenocarcinoma<br>– Former: 0.9 (0.6–1.4)<br>– Current: 1.0 (0.6–1.7)<br>• Squamous cell carcinoma<br>– Former: 2.1 (1.0–4.4)<br>– Current: 1.4 (0.7–2.8)<br>• Gastric cardia adenocarcinoma<br>– Former: (0.9 (0.6–1.4)<br>– Current: 1.4 (0.8–2.2) | 1994–2007; Swedish Oesophageal and Cardia Cancer Study; current includes smoking within 2 years of diagnosis |
| Talamini et al. 2008 | • 268 NHL patients | Ever/Never | • 1-19 cpd: 1.22 (0.80–1.86)<br>• ≥20 cpd: 1.70 (1.06–2.73)<br>• Duration of smoking (years)<br>– <30: 1.41 (0.89–2.23)<br>– ≥30: 1.32 (0.85–2.05) | 1983–2002 |
| Tian et al. 2008 | • 233 Stave I–IV NSCLC patients | Ever/Never | • 1.74 (0.90–3.39) | |
| Toyooka et al. 2008 | • 408 advanced or recurrent NSCLC patients | Ever/Never | • ≥20 Pack-years: 1.0 (referent)<br>• <20 Pack-years: 0.95 (0.62–1.46)<br>• Never: 0.83 (0.58–1.20) | Chart review; analyses based upon pack year |
| Chansky et al. 2009 | • 2,467 stage I–IIIA NSCLC patients | C/F/N | • Current vs. former: 1.21, p <0.0001<br>• Current vs. never: 1.41, p = 0.0017<br>• Former vs. never: 1.16, p = 0.16 | 1990–2000; patients treated with surgery and part of IASLC Lung Cancer Staging Project |
| Coker et al. 2009 | • 2,661 women with cervical cancer | Current/ Notcurrent | • 1.35 (1.17–1.56) | 1995–2005; reference category includes never and former smokers |
| Duffy et al. 2009 | • 504 head neck cancer patients | C/F/N | • Former: 2.02 (1.16–3.51)<br>• Current: 2.36 (1.28–4.37) | 2003–2008; structured health habits assessment |

**Table 6.28*S* Continued**

| Study | Design/population | Smoking definition | Findings (all comparisons are vs. never unless otherwise specified) | Comments |
|---|---|---|---|---|
| Guo et al. 2009 | • 327 stage I–III NSCLC patients | Heavy/ Non-heavy | • 61 or less: 1.0 (referent)<br>• >61 Pack-years: 1.41 (1.03–1.94) | Referent group includes ever and never smokers; patients pooled from 4 lung cancer cohorts |
| Hayashibara et al. 2009 | • 626 NSCLC patients | Ever/Never | • 1.20 (0.94–1.52) | 2002–2007; chart review; patients treated with gefitinib |
| Hotta et al. 2009 | • 365 NSCLC patients | Ever/Never | • Males: 1.012 (1.00–1.02)<br>• Females: 1.007 (0.98–1.03) | 2000–2003; risks stated per pack year; patients treated with gefitinib |
| Hsu et al. 2009a | • 695 stage I–IV NSCLC patients | Ever/Never | • 1.27 (0.97–1.65) | 2002–2006; more than 50% of patients were stage IV |
| Huang et al. 2009 | • 671 postmenopausal females with primary lung cancer | Ever/Never | • 1.41 (p = 0.03) | 1995–2005; chart review |
| Koch et al. 2009 | • 289 Stage IIIB–IV NSCLC patients | Current/ Noncurrent | • 1.50 (1.11–2.02) | 2002–2007; chart review; patients treated with chemotherapy |
| Li et al. 2009b | • 325 stage I NSCLC patients | Ever/Never | • 1.56 (0.882–2.759) | 1998–2003; chart review; patients treated with surgery |
| Lin et al. 2009 | • 109 thoracic esophageal SCC patients | Ever/Never | • 2.47 (1.36–4.51) | 2000–2004; smoking not clearly defined in analysis; chart review; patients treated with surgery |
| Marks et al. 2009 | • 2,818 HLA identical sibling or matched unrelated donor allogeneic transplants for CML | Ever (High dose, low dose)/Never | • HLA-identical sibling donor group<br>– Low dose: 1.01 (0.84–1.22)<br>– High dose: 1.44 (1.07–1.93)<br>• Unrelated donor group<br>– Ever: 0.96 (0.75–1.21) | 1990–2004 |
| Myrdal et al. 2009 | • 4,791 NSCLC patients | C/F/N | • Former: 1.15 (1.01–1.29)<br>• Current: 1.30 (1.15–1.46) | 1995–2003; current includes patients who quit <12 months prior |
| Mayne et al. 2009 | • 264 Stage I–II head/neck cancer patients | C/F/N | • Current at diagnosis: 4.91 (0.67–35.98)<br>• Current after diagnosis: 1.83 (0.85–3.94) | 1991–1998; randomized beta-carotene chemoprevention trial |
| Ou et al. 2009a | • 20,140 NSCLC patients | Ever/Never | • 1.07 (1.01–1.13) | 1991–1995; chart review; patients from California Cancer Surveillance Program |
| Ou et al. 2009b | • 3,428 extensive stage SCLC patients | Ever, never | • 1.31 (1.06–1.62) | 1991–2005; chart review; patients from California Cancer Surveillance Program |

**Table 6.28*S* Continued**

| Study | Design/population | Smoking definition | Findings (all comparisons are vs. never unless otherwise specified) | Comments |
|---|---|---|---|---|
| Chang et al. 2010 | • 110 NSCLC patients | Ever/Never | • 1.86 (1.09–3.17) | 2006–2008; chart review |
| Chen et al. 2010c | • 284 limited stage SCLC | Current/ Noncurrent | • Current: 1.0 (referent)<br>• Former/Never: 0.72 (0.52–1.00)<br>• Quit at or after diagnosis: 0.55 (0.38–0.79) | 1997–2007; chart review; continued smoking is referent group |
| Chen et al. 2010d | • 203 stage IIIB–IV NSCLC patients age 80+ at diagnosis | Ever/Never | • Univariate: 1.44 (1.06–1.95)<br>• Multivariate: NS | 2000–2006; chart review |
| Fontaine et al. 2010 | • 412 stage I–III NSCLC patients | Ever/Never | • 1.82 (p = 0.007) | 2001–2009; patients taking aspirin and treated with surgery |
| Geyer et al. 2010 | • 471 NHL patients | C/F/N | • Former: 1.59 (1.12–2.26)<br>• Current: 1.50 (0.97–2.29) | 1998–2000; follow-up structured health behavior interview |
| Hellmann et al. 2010 | • 528 breast cancer patients | C/F/N | • Former: 1.04 (0.88–1.23)<br>• Current: 1.16 (1.05–1.29) | 1976–2003, Copenhagen City Heart Study; repeated structured questionnaires |
| Hung et al. 2010 | • 525 stage IB NSCLC patients | Smoking | • 1.003 (0.999–1.007) | 1980–2000; analysis of risk according to pack year; patients treated with surgery |
| Ioffe et al. 2010 | • 130 Stage III-IV epithelial ovarian cancer patients | Current/ Notcurrent | • 2.25 (1.30–3.87) | 1996–2003; patients treated with cytoreductive surgery; chart review current defined as smoking at time of surgery |
| Janjigian et al. 2010 | • 2,010 stage IIIB–IV NSCLC patients | Ever/Never | • 15 or less vs. never: 1.15 (0.92–1.43)<br>• >15 vs. 15 or less: 1.23 (1.03–1.48)<br>• >15 vs. never: 1.42 (1.20–1.67) | 2003–2006; ever according to pack-years |
| Kawaguchi et al. 2010b | • 26,957 NSCLC patients | Ever/Never | • 1.07 (1.01–1.31) | 1990–2005; patients from National Hospital Organization Study Group for Lung Cancer |
| Kim et al. 2010 | • 342 NSCLC patients | Ever/Never | • 1.41 (0.99–2.00) | 2006–2008; chart review; patients treated with erlotinib or gefitinib |
| Lee et al. 2010b | • 237 stage I–II NSCLC patients | Smoker | • 1.31 (0.73–2.35) | 2003–2007; smoking not clearly defined in analysis; patients treated with surgery |
| McCleary et al. 2010 | • 1,045 participants with stage III colon cancer | C/F/N | • Former: 1.17 (0.87–1.57)<br>• Current: 1.38 (0.87–2.18) | Data from CALGB 89803 randomized trial treated with 5-FU/leucovorin +/- irinotecan |
| Meguid et al. 2010 | • 4,536 NSCLC patients | C/F/N | • Never: 1.0 (referent)<br>• Current: 1.08 (0.95–1.22) | 1975–2004 |

**Table 6.28*S* Continued**

| Study | Design/population | Smoking definition | Findings (all comparisons are vs. never unless otherwise specified) | Comments |
|---|---|---|---|---|
| Naito et al. 2010 | • 826 stage T1a–T2a NSCLC patients | Ever/Never | • <30 Pack-years: 1.0 (referent)<br>• ≥30 Pack-years: 1.58 (0.92–2.71) | 1993–2003; chart review; analysis according to pack year history |
| Olson et al. 2010 | • 475 pancreatic cancer patients | C/F/N | • Resected patients<br>– Former: 0.83 (0.34–2.03)<br>– Current: 0.99 (0.58–1.69)<br>• Unresected patients<br>– Former: 1.00 (0.73–1.36)<br>– Current: 0.79 (0.52–1.20) | 2001–2006; Familial Pancreatic Cancer Registry; current smoking included patients who smoked in the year prior to diagnosis |
| Sardari et al. 2010 | • 239 NSCLC patients | Current/ Noncurrent | • 1.46 (1.04–2.04) | 1991–2001; patients treated with surgery |
| Shitara et al. 2010 | • 363 patients with SCC of the esophagus | Heavy (≥20 Pack-years)/Not Heavy | • 1.73 (1.12–2.68) | 2001–2005; referent category combined never smokers + smokers with <20 Pack-years history; patients treated with RT+chemotherapy or surgery |
| Syrigos et al. 2010 | • 1,725 stage IIIB–IV NSCLC patients | Ever/Never | • Nonsquamous histology: 1.75 (1.42–2.15)<br>• Squamous histology: 1.50 (0.94–2.42) | Patients enrolled on randomized trial of chemotherapy |
| Ali et al. 2011 | • 170 inflammatory bowel disease patients from 22,325 CRC cases | C/F/N | • Current vs. former: 1.15 (1.07–1.23)<br>• Current vs. never: 1.20 (1.13–1.28) | 1994–2005; Irish National Cancer Registry |
| Dandona et al. 2011 | • 355 pancreatic cancer patients | C/F/N | • Former: 1.07 (0.80–1.44)<br>• Current: 1.07 (0.78–1.48) | 1995–2000; patients treated with surgery; chart review. |
| Dragun et al. 2011 | • 11,914 stage 0–II breast cancer patients | Ever/Never | • 1.43 (1.28–1.60) | 1998–2007; Kentucky Tumor Registry; chart review; patients treated with breast conservation surgery |
| Ehlers et al. 2011 | • 148 leukemia patients | C/F/N | • Former: 1.17 (0.721.91)<br>• Current: 1.75 (1.00–3.06) | 1999–2005; patients treated with hematopoietic stem cell transplant; current includes smoking within the prior year; chart review |
| Farshadpour et al. 2011 | • 2,012 head/neck cancer patients | Current/ Noncurrent | • 1.50 (1.16–1.93) | 1980–2004; smoking combined with drinking in analysis |
| Kato et al. 2011 | • 358 stage IA–IIIB NSCLC patients | Ever/Never | • Univariate: 1.63 (1.03–2.57)<br>• Multivariate: 0.86 (0.49–1.48) | 1992–2004; chart review |

**Table 6.28*S* Continued**

| Study | Design/population | Smoking definition | Findings (all comparisons are vs. never unless otherwise specified) | Comments |
|---|---|---|---|---|
| Kenfield et al. 2011 | • 5,366 prostate cancer patients | C/F/N | • Former: 1.23 (1.10–1.37)<br>• Current: 2.28 (1.87–2.80) | Health Professionals Follow-Up Study; structured questionnaire every 2 years |
| Kountourakis et al. 2011 | • 49 patients with T2 esophageal cancer | Smoker/ Nonsmoker | • 5.93 (1.32–26.57) | 1997–2009; patients treated with surgery, RT, and chemotherapy |
| Kroeger et al. 2011 | • 802 renal cell carcinoma patients | Ever/Never | • 1.36 (1.13–1.64) | 1989–2007; chart review |
| Kvale et al. 2011 | • Cardiovascular Health Study<br>• 789 elderly cancer patients matched with 3,119 elderly noncancer patients | Current/ Noncurrent | • 1.72 (1.23–2.42) | |
| Li et al. 2011 | • 1,139 lung cancer patients | Ever/Never | • 1.28 (1.04–1.58) | 1998–2004; chart review |
| Maeda et al. 2011a | • 2,295 stage I–III NSCLC patients | Ever/Never | • Stage I: 1.83 (1.27–2.64)<br>• Stage II: p = 0.74<br>• Stage III: p = 0.90 | 1992–2006; ever smoking defined as >43 Pack-years |
| Maeda et al. 2011a | • 1,870 stage I–II NSCLC patients | Ever/Never | • 1.77 (p <0.001) | 1992–1997; 5-year mortality; chart review; patients treated with curative surgery |
| Ngô et al. 2011 | • 257 patients with cervical cancer <4 cm in diameter | Current smokers >10 cpd vs. ≤10 cpd | • 3.07 (1.58–5.97) | 1985–2008; referent category includes light current smokers + former + never smokers; patients treated with preoperative brachytherapy and surgery; 5-year mortality |
| Phipps et al. 2011 | • 2,264 colorectal cancer patients | C/F/N | • Former: 1.26 (1.07–1.49)<br>• Current: 1.51 (1.24–1.83) | 1998–2007; structured questionnaire post-diagnosis |
| Richards et al. 2011 | • 423 Stage I-III colorectal cancer patients | C/F/N | • 1.30 (1.07–1.57) | 1997–2007; smoking not clearly defined but appears to be current; patients treated with curative surgery |
| Richey et al. 2011 | • 188 metastatic renal cell cancer patients | Current/ Noncurrent | • 1.71 (1.06–2.78) | 2003–2009; patients treated with targeted therapy and no surgery; chart review; reference category includes never and former smokers |
| Schlumbrecht et al. 2011 | • 194 low grade serous adenocarcinoma of the ovary | Current/ Noncurrent | • 1.57 (0.99–2.48) | 1977–2009; reference category includes former and never smokers |

**Table 6.28*S* Continued**

| Study | Design/population | Smoking definition | Findings (all comparisons are vs. never unless otherwise specified) | Comments |
|---|---|---|---|---|
| Sfakianos et al. 2011 | • 623 consecutive patients with high grade superficial, carcinoma in situ, or T1 invasive bladder cancer | C/F/N | • Former: 1.20 (0.82–1.74)<br>• Current: 1.03 (0.63–1.68) | 1994–2008; chart review; patients treated with BCG and surgery |
| Taira et al. 2011 | • 1,656 prostate cancer patients | C/F/N | • Former: 1.43 (p = 0.017)<br>• Current: 2.86 (p <0.001) | 1995–2006; treated with brachy-therapy +/- androgen deprivation therapy +/- external beam RT |
| Yafi et al. 2011 | • 2,287 bladder cancer cases | Smoker/ Nonsmoker | • 1.31 (1.05–1.63) | 1998–2008; chart review; treated with radical cystectomy |
| Bostrom et al. 2012 | • 564 bladder cancer patients | Ever/Never | • 1.4 (1.1–1.8) | 1991–2008; treated with radical cystectomy; chart review |
| Gajdos et al. 2012 | • 20,413 gastrointestinals, thoracic, and urologic cancer patients | C/F/N | • Gastrointestinal<br>– Former: 1.22 (1.08–1.38)<br>– Current: 1.62 (1.43–1.85)<br>• Thoracic<br>– Former: 1.19 (0.92–1.54)<br>– Current: 1.50 (1.17–1.92)<br>• Urologic<br>– Former: 1.04 (0.77–1.41)<br>– Current: 1.19 (0.90–1.58) | VA Surgery Quality Improvement Program; 1-year mortality; patients treated with major surgery |
| Gillison et al. 2012 | • 502 stage III–IV head/neck cancer patients | Current/ Noncurrent | • 2.34 (1.56–3.50) | Data from RTOG 9003 and RTOG 0129 randomized phase III trials treating with RT +/- chemotherapy; reference category includes never and former smokers |
| Gridelli et al. 2012 | • 780 stage IIIB-IV NSCLC patients | Ever/Never | • 1.27 (1.06–1.54) | Patients treated on randomized TORCH trial |
| Hoff et al. 2012 | • 232 head/neck cancer patients treated with RT | Current/ Noncurrent | • 2.01 (1.28–3.15) | 1983–1991; reference category includes never and former smokers |
| Holgersson et al. 2012 | • 1,146 NSCLC patients | C/F/N | • Former: 1.10 (0.82–1.45)<br>• Current: 1.06 (0.80–1.41) | 1990–2000; chart review; patients treated with curative RT |
| Hung et al. 2012 | • 756 stage I NSCLC patients | C/F/N | • Never: 1.0 (referent)<br>• 1–20 Pack-years: 1.48 (1.11–1.98)<br>• >20 Pack-years: 1.99 (1.60–2.47) | 1980–2010; analysis according to Pack-years history; patients treated with lobar resection |

**Table 6.28*S* Continued**

| Study | Design/population | Smoking definition | Findings (all comparisons are vs. never unless otherwise specified) | Comments |
|---|---|---|---|---|
| Kawaguchi et al. 2012 | • 2,966 stage IIIB-IV NSCLC patients ≥70 years old | C/F/N | • Current: 1.0 (referent)<br>• Former:<br>– 70–74: 0.91 (0.80–1.04)<br>– 75–79: 1.06 (0.92–1.22)<br>– 80+: 1.08 (0.90–1.29)<br>• Never:<br>– 70–74: 0.78 (0.66–0.93)<br>– 75–79: 0.80 (0.66–0.97)<br>– 80+: 0.99 (0.80–1.21) | 1990–2005; current smoking is referent group; analysis according to age; patients treated with chemotherapy |
| Kawakita et al. 2012 | • 222 patients with oral cavity cancer | Current/ Noncurrent | • Light smokers: 1.0 (referent)<br>• Moderate: 2.44 (1.07–5.57)<br>• Heavy: 2.66 (0.97–7.33) | 2001–2005; referent category is light smokers |
| Lee et al. 2012a | • 924 stage IIIB–IV NSCLC patients | Ever/Never | • Not significant (Forest plot) | 2006–2008; patients enrolled on phase III ZEPHYR trial in patients who failed EGFR therapy |
| Lee et al. 2012b | • 670 stage IIIB-IV NSCLC patients | C/F/N | • Former: 1.09 (0.85–1.41)<br>• Current: 1.56 (0.88–2.78) | Patients treated with erlotinib on TOPICAL trial |
| Liu et al. 2012 | • 282 women <40 years old with lung cancer | Current/ Noncurrent | • 3.32 (1.73–8.79) | 1985–2007 |
| Maeda et al. 2012 | • 1,070 stage IA lung cancer patients | Ever/Never | • 20 or less: 1.0 (referent)<br>• >20: 1.83 (1.29–2.57) | 1992–1997; analysis according to Pack-years history; Patients treated with curative surgery |
| Nawa et al. 2012 | • 210 lung cancer patients | Ever/Never | • 4.7 (1.3–16.5) | 1998–2006; 5-year mortality; smoking not clearly defined in analysis; patients in chemotherapy screening program |
| Paik et al. 2012 | • 675 NSCLC patients | Ever/Never | • 1.9 (1.4–2.5) | 2009–2010 |
| Pirker et al. 2012 | • 1,125 stage IIIB-IV NSCLC patients | C/F/N | • Current: 1.0 (referent)<br>• Former: 0.86 (0.73–1.02)<br>• Never: 0.72 (0.58–0.88) | Patients enrolled on phase III trial adding cetuximab to chemotherapy |
| Ryu et al. 2012 | • 569 stage I NSCLC patients | Ever/Never | • 1.18 (0.76–1.83) | 1997–2005; patients treated with curative surgery |
| Toffalorio et al. 2012 | • 467 stage T2N0 NSCLC patients | C/F/N | • Former: 1.45 (0.70–3.00)<br>• Current: 1.61 (0.75–3.46) | 1998–2009; chart review; patients treated with surgery |

**Table 6.28*S* Continued**

| Study | Design/population | Smoking definition | Findings (all comparisons are vs. never unless otherwise specified) | Comments |
|---|---|---|---|---|
| Varadarajan et al. 2012 | • 280 acute myeloid leukemia patients | Ever/Never | • 1.64 (1.21–2.21) | 1990–2008; chart review; patients treated with high dose cytarabine and idarubicin |
| Wang et al. 2012 | • 301 stage II–IIIA NSCLC patients | Ever/Never | • 0.89 (0.67–1.19) | 2000–2006; chart review; patients treated with surgery |
| Dahlstrom et al. 2013 | • 2,299 oropharyngeal cancer patients. | Ever/never | • 1955–1994 cohort: 1.4 (1.2–1.7)<br>• 1995–2004 cohort: 2.3 (1.7–3.2) | 1955–2004; chart review |
| Ferketich et al. 2013 | • 4,200 NSCLC patients | Current, recent quit, former, never | • Current: 1.0 (referent for each Stage)<br>• Stage I-II:<br>– Never: 0.47 (0.26–0.85)<br>– Former <12 months: 0.80 (0.51–1.24)<br>– Former >12 months: 0.84 (0.65–1.08)<br>• Stage III:<br>– Never: 0.51 (0.38–0.68)<br>– Former <12 months: 0.79 (0.59–1.07)<br>– Former >12 months: 0.85 (0.70–1.03)<br>• Stage IV: (stratified by age)<br>– Never: significant for all under age 85<br>– Former: significant for all under age 65 | Patients from NCCN Database Project |
| Johnson et al. 2013 | • 1,036 stage IV lung cancer patients | Ever/Never | • Univariate: 1.18 (1.01–1.37)<br>• Multivariate: 1.00 (0.85–1.18) | 2002–2009; chart review; patient analysis corrected for *EGFR* and *KRAS* mutations |
| Poullis et al. 2013 | • 2,485 stage I-III NSCLC patients | Current/ Noncurrent | • 1.33 (1.14–1.54) | 2001–2011; patients treated with curative surgery |
| Tanaka et al. 2013 | • 244 stage III–IV NSCLC patients | Ever/Never | • 1.67 (1.13–2.47) | 2004-2009; smoking not well defined in analysis; patients treated with chemotherapy |
| Warren et al. 2013 | • 5,185 cancer patients with 13 types of malignancy. | Current/recent quit/ former/never | • Current vs. never: 1.38 (1.23–1.54)<br>• Current vs. former: 1.29 (1.17–1.42)<br>• Current vs. recent quit: 1.17 (1.03–1.32) | 1982–1998; structured tobacco assessment within 30 days of diagnosis; referent category = current smokers |

*Note:* **C/F/N** = current/former/never; **CALCB** = cancer and leukemia group B; **CML** = chronic myelogenous leukemia; **cpd** = cigarettes per day; **5-FU** = 5-fluorouracil; **GOG** = Gynecologic Oncology Grpup; **HLA** = human leukocyte antigen; **IASLC** = International Association for the Study of Lung Cancer; **NSCLS** = non-small-cell lung cancer; **pack-years** = the number of years of smoking multiplied by the number of packs of cigarettes smoked per day; **RT** = radiotherapy; **RTOG** = Radiation Therapy Oncology Group.

**Table 6.29*S* Associations between smoking and overall survival in cancer patients**

| Study | Design/population | Smoking definition | Findings (all comparisons are vs. never unless otherwise specified) | Comments |
|---|---|---|---|---|
| Herr et al. 1990 | • 122 CML patients, Retrospective | Smoker/ nonsmoker | • 0.74 (p = 0.02) | 1968–1987; median survival; chart review; smoking defined as current tobacco use of ≥5 Ppck years within the 10 years prior to diagnosis |
| Hopkins et al. 1991 | • 345 stage IB cervical cancer patients | Smoking history | • Reported as not statistically significant in the text. (p. 1521) | 1970–1985; chart review; smoking not clearly defined |
| Harpole et al. 1995 | • 271 consecutive Stage I NSCLC patients | Pack-years | • 0: 59% (p = 0.63)<br>• 1–20: 63%<br>• 21–50: 60%<br>• >50: 55% | 1980–1988; 10-year survival; chart review |
| Fountzilas et al. 1997 | • 154 Stage III–IV head/neck cancer patients | Ever/never | • 0.66 (p = 0.03) | 1984–1991; median survival; patients treated with induction chemotherapy followed by surgery or RT |
| Holli et al. 1999 | • 792 Stage I–IV NSCLC patients | Pack-years | • <25: 1.00<br>• 25–40: 0.84 (0.61–1.15)<br>• >40: 0.94 (0.68–1.29) | 1983–1987; overall survival; chart review |
| Suzuki et al. 1999 | • 430 Stage I NSCLC patients | Pack-years | • 0–5 pack-years: 89.8% (p = 0.002)<br>• 5+ pack-years: 79.1% | 1987–1997; 5-year survival; chart review; patients treated with surgery |
| Oh et al. 2000 | • 148 renal cell cancer patients | Ever/never | • "When stratified by metastatic status, however, a significant difference in overall survival was noted between smokers and nonsmokers among patients with Stage M0 (P = 0.039)." (p. 32) | 1980–1994; chart review; patients treated with surgery |
| de Graeff et al. 2001 | • 208 head/neck cancer patients | Current smoking amount | • Reported as not statistically significant in the text. (p. 336) | 1994–2006; patients treated with surgery and/or RT |
| Chelghoum et al. 2002 | • 642 acute myeloid leukemia patients | Ever/never | • 0-20 pack-years: 1.0 (referent)<br>• ≥20 pack-years: 0.77 (p = 0.02)<br>• Duration smoked (years):<br>– 0–30: 1.0 (referent)<br>– ≥30: 0.65 (p = 0.004) | 1984–1998; pack-years and median survival; structured tobacco assessments by patients or relatives |
| Ganti et al. 2002 | • 308 pancreatic cancer patients, Retrospective | Ever/Never | • 1.14 (p = 0.97) | 1985–2001; median survival; chart review; smoking not clearly defined in analysis |

**Table 6.29*S* Continued**

| Study | Design/population | Smoking definition | Findings (all comparisons are vs. never unless otherwise specified) | Comments |
|---|---|---|---|---|
| Yang et al. 2002 | • 250 Stage I–IV NSCLC patients | C/F/N with pack-years | • Never: 83% (p=0.078)<br>• Current 40+ pack-years: 71%<br>• Current <40 pack-years: 74%<br>• Past 40+ pack-years: 82%<br>• Past <40 pack-years: 65% | 1997–1999; 1-year survival |
| Lo et al. 2003 | • 378 oral cavity cancer patients | Ever/Never | • 0.92 (p <0.01) | 1975–96; 5-year survival; chart review; smoking not clearly defined; patients treated with surgery +/- RT +/- chemotherapy |
| Wu et al. 2003 | • 321 Stage I NSCLC patients | Pack-years | • 20 or less: 40.7%<br>• >20: 26.4% (p<0.0007) | 1980–1990; 10-year survival; chart review |
| Fox et al. 2004 | • 237 Stage I–III NSCLC patients | Current, non-current | • Stage I–II<br>– Current: 13.7 mo<br>– Non-current: 27.9 mo (p = 0.01)<br>• Stage III<br>– Current: 19.5 mo<br>– Non-current: 17.7 mo (p = 0.46) | 1991–2001; median survival; chart review; current smoking include patients who quit within 12 months of RT; patients treated with RT |
| Gorsky et al. 2004 | • 322 patients with tongue cancer | Smoker/ nonsmoker | • Reported as not statistically significant in the text. (p. 549) | 1979–1994; chart review; smoking not clearly defined in analysis |
| Iizasa et al. 2004 | • 402 Stage I lung cancer patients | Pack-years | • 30+: 47.9%<br>• <30: 75% (p = 0.0012) | 1985–1997; 10-year survival; patients treated with surgery |
| Oefelein et al. 2004 | • 222 advanced prostate cancer including 133 hormone refractory patients | C/F/N | • Never: 1.0 (referent)<br>• Former: 0.78<br>• Current: 0.63 (p = 0.00001) | 1987–2003; median survival; chart review |
| Yamamoto et al. 2004 | • 207 Stage I–IIIA NSCLC | Smoking habit | • Yes: 75.1%<br>• No: 71.8% (not significant) | 1990–1995; smoking not clearly defined; chart review. |
| Brumund et al. 2005 | • 270 patients with T1–T3 true vocal cord cancer | Pack year | • Reported as not statistically significant in the text. (p. 319) | 1975–2000; chart review |

**Table 6.29*S* Continued**

| Study | Design/population | Smoking definition | Findings (all comparisons are vs. never unless otherwise specified) | Comments |
|---|---|---|---|---|
| Herbst et al. 2005 | • 1079 Stage IIIB–IV NSCLC patients | C/F/N | • Chemotherapy + Erlotinib:<br>– Current: 8.4 mo,<br>– Former: 10.0 mo<br>– Never: 22.5 mo (p=0.01)<br>• Chemotherapy alone:<br>– Current: 9.1 mo<br>– Former: 10.9 mo<br>– Never: 10.1 mo | 2001–2002; median survival; TRIBUTE trial; randomized trial of chemotherapy +/- Erlotinib |
| Videtic et al. 2005 | • 215 limited stage SCLC | Current | • Survival (p=0.0046):<br>– Male smoker: 9.1%<br>– Male nonsmoker: 22.1%<br>– Female smoker: 21.6%<br>– Female nonsmoker: 38.7% | 1989–1999; overall survival; chart review; patients treated with CRT; smoking defined as smoking during CRT |
| Donat et al. 2006 | • 1,159 renal cell carcinoma patients | Ever/never | • 0.91 (p = 0.10) | 1995–2003; 5-year survival; patients treated with surgery |
| Ganti et al. 2006 | • 498 women with lung cancer | Ever/never | • Ever, HRT+: 39 mo<br>• Ever, HRT-: 73 mo<br>• Never, HRT+: 92 mo<br>• Never, HRT-: 98 mo | 1994–1997; median survival; chart review; ever defined as 5+ pack-years |
| Gautschi et al. 2006 | • 244 Stage I–IV NSCLC patients | Pack-years | • "The extent of smoking (<40 pack-years versus >40 pack-years) correlated neither with response to chemotherapy, nor with survival (data not shown)." p. 306 | 2001–2003 |
| Guntinas-Lichius et al. 2006 | • 69 patients with unknown primary of the head/neck | Smoker/ nonsmoker | • 0.36 (p = 0.02) | 1987–2002; 5-year survival; chart review; smoking not clearly defined |
| Lee et al. 2006 | • 575 stage IIIB–IV patients | Ever/never | • Never: 15.1 mo<br>• Ever: 6.1 mo (p<0.001)<br>• Multivariate: p=0492 (pg. 343) | 2002–2005; median survival; chart review; patients treated with gefitinib |
| Tsuchiya et al. 2006 | • 322 Stage IA NSCLC patients | Pack-years | • <40 pack-years: 87.9%<br>• 40+ pack-years: 80.1% (p=0.442) | 1979–2004; 5-year survival; chart review; patients treated with surgery; referent group includes smokers and nonsmokers |

**Table 6.29*S* Continued**

| Study | Design/population | Smoking definition | Findings (all comparisons are vs. never unless otherwise specified) | Comments |
|---|---|---|---|---|
| Gillespie et al. 2007 | • 325 head/neck cancer patients | Smoker/ nonsmoker | • 1.24 (0.60–2.57) | Chart review; case control study for COX2 inhibitors; smoking not clearly defined in analysis |
| Hidaka et al. 2007 | • 185 esophageal cancer patients | Brinkman index ≥800 vs. <800 | • 0.95 (p = 0.53) | 1978–2005; 5-year survival; referent category includes never and former smokers with up to 20 pack year history; patients treated with surgery |
| Satouchi et al. 2007 | • 221 NSCLC patients | Ever/never | • 0.41 (0.29–0.58) | 2002–2005; chart review; patients treated with gefitinib |
| Yildizeli et al. 2007 | • 218 NSCLC patients | Current/ noncurrent | • p=0.45 (pg. 99) | 1981–2005; chart review; patients treated with sleeve resection |
| Bryant and Cerfolio 2008 | • 186 African American men with NSCLC matched with 744 White men | Ever/never | • "Smoking rate and time until presentation for treatment were the only independent predictors on Cox Hazards analysis (p=0.007) for African American men." (p. 713) | 1997–2007 |
| Florescu et al. 2008 | • 731 stage IIIB–IV patients | C/F/N | • Former: 0.82 (p <0.001)<br>• Current: 0.53 ( p <0.001) | Patients enrolled on BR21 trial of patients who failed prior therapy treated with erlotinib |
| Rajappa et al. 2008 | • 294 stage IIIB–IV NSCLC patients | Ever/never | • 0.78 (p = 0.0074) | 2002–2006; median survival |
| Sakao et al. 2008 | • 121 NSCLC patients with tumors <2 cm | Ever/never | • 0.84 (p = 0.05) | 1996–2006; 5-year survival; chart review; patients treated with surgery |
| Spigel et al. 2008 | • 229 stage IIIB-IV NSCLC patients | Ever/never | • 0.71 (no statistics) | 2004; analysis according to pack-years; patients treated on phase III trial of erlotinib |
| Bostrom et al. 2009 | • 248 bladder cancer patients | Ever/never | • 0.71 (p = 0.03) | 1986–2005; chart review; 10-year survival; patients treated with radical cystectomy |
| Fortin et al. 2009 | • 1,871 head/neck cancer patients | C/F/N | • Former: 0.81<br>• Current: 0.74 (p = 0.0005) | 1989–2006; 5-year survival; chart review; patients treated with RT +/- chemotherapy +/- surgery |

**Table 6.29*S* Continued**

| Study | Design/population | Smoking definition | Findings (all comparisons are vs. never unless otherwise specified) | Comments |
|---|---|---|---|---|
| Gupta et al. 2009 | • 203 stage III–IV NSCLC patients | Ever/Nnver | • 0.22 (0.19–0.61) | 2006–2008; 2-year survival; structured tobacco interview |
| Hsu et al. 2009b | • 217 stage I NSCLC patients | Smoker/ Nonsmoker | • 0.89 (p = 0.460) | 2000–2006; 5-year survival; chart review; smoking not clearly defined |
| Ahn et al. 2010 | • 13,469 NSCLC patients | Ever/never | • Korean: 0.87 (p = 0.0141)<br>• White: 0.93 (p = 0.0397) | 1995–2008; 2-year survival; analyzed according to race; chart review; California Cancer Surveillance Program |
| Ang et al. 2010 | • 721 Stage III–IV head neck cancer patients | Pack-years | • Smoking decreased survival by 1% per pack year (p = 0.002) | Data from 2 randomized cancer treatment trials |
| Chen et al. 2010b | • 122 stage III–IV NSCLC patients | Ever/never | • 0.57 (p = 0.010) | 2002–2007; chart review; patients treated with gefitinib monotherapy |
| Jamal et al. 2010 | • 94 unresectable pancreatic cancer patients | Smoker/ nonsmoker | • 0.39 (p = 0.09) | 2001–2006; chart review; smoking within 5 years of diagnosis |
| Kawaguchi et al. 2010a | • 28,517 NSCLC patients | Ever/never | • Japanese: 0.74 (p <0.0001)<br>• United States: 0.92 (p = 0.1282) | 1991–2007; 2-year survival; chart review |
| Liao et al. 2010 | • 409 unresectable NSCLC patients | Current/ noncurrent | • 0.93 (0.69–1.25) | 1999–2006; chart review; patients treated with RT |
| Liu et al. 2010b | • 698 patients with oral cavity cancer | Ever/never | • 1.13 (p = 0.24) | 1995–2005; 5-year survival; chart review; patients treated with surgery +/- adjuvant therapy |
| Na et al. 2010 | • 162 female stage IIIB–IV NSCLC | Ever/never | • 1.01 (p = 0.291) | 2002–2008; median survival; chart review; patients treated with gefitinib monotherapy |
| Nugent et al. 2010 | • 111 stage IB2–IV cervical cancer patients | Ever/never | • Reported as not statistically significant in the text. (p. 440) | 2003–2007; chart review; patients treated with RT + chemotherapy |
| Sakao et al. 2010 | • 106 NSCLC patients with multilevel nodal metastases | Ever/never | • 0.57 (p = 0.12) | 1988–2007; 5-year survival; chart review; patients treated with surgery |
| Wang et al. 2010b | • 257 stage I lung cancer patients | Smoking | • 0.91 (p = 0.154) | 1995–2000; 5-year survival; patients treated with surgery |
| Yang et al. 2010 | • 1,725 stage IIIB–IV NSCLC patients | Ever/never | • 0.93 (0.81–1.05) | Patients enrolled on randomized trial of chemotherapy |

**Table 6.29*S* Continued**

| Study | Design/population | Smoking definition | Findings (all comparisons are vs. never unless otherwise specified) | Comments |
|---|---|---|---|---|
| Chen et al. 2011a | • 202 head/neck cancer patients | Current/ Nnncurrent | • 0.45 (p <0.001) | 1998–2008; chart review; patients treated with RT +/- surgery |
| Li et al. 2011 | • 1,214 stage IIIB–IV NSCLC patients | C/F/N | • Former: 0.905 (0.65–1.26)<br>• Current: 0.955 (0.57–1.60) | Patients treated with gemcitabine-based chemotherapy |
| Michigan et al. 2011 | • 257 localized renal cell carcinoma patients | Smoker/ nonsmoker | • 0.54 (0.06–4.93) | 2006–2010; smoking not clearly defined; patients treated with surgery |
| Roxburgh et al. 2011 | • 302 CRC patients | Ever/never | • 0.81 (p = 0.07) | 1997–2005; 5-year survival; patients treated with surgery |
| Santini et al. 2011 | • 248 metastatic breast cancer patients | C/F/N | • Reported as not statistically significant in the text. (p. 1547–8) | 2004–2007; chart review; current included patients who quit within 6 months; patients treated with trsztuzumab +/- chemotherapy |
| Simsir et al. 2011 | • 140 patients with urothelial or TCC of the upper urinary tract | Ever/never | • 0.68 (p = 0.02) | 2000–2007; 5-year survival; chart review; patients treated with surgery |
| Thompson et al. 2011 | • 276 head/neck cancer patients who survived at least 2 years | Current/ noncurrent | • 0.91 (p = 0.04 univariate, 0.17 multivariate) | 2001–2008; 5-year survival; current defined as smoking 2 years after treatment |
| Arrieta et al. 2012 | • 914 stage I–IV lung cancer patients | Ever/never | • Unadjusted 0.56 (p = 0.002)<br>• Adjusted: 1.04 (0.74–1.5) | 2007–2010; median survival |
| Jerjes et al. 2012 | • 67 oral cavity cancer patients treated with surgery | Smoking after treatment | • Smoking cessation: 1.0 (referent)<br>• Reduced smoking: 0.98<br>• Smoker 20+ CPD: 0.14(p <0.001) | 1998–2003; 5-year survival |

*Note*: **C/F/N** = current/former/never; **CML** = chronic myelogenous leukemia; **cpd** = cigarettes per day; **HRT** = hormone replacement therapy; **NSCLS** = non-small-cell lung cancer; **RT** = radiotherapy; **TCC** = transitional cell carcinoma.

**Table 6.30*S* Associations between smoking and cancer-related mortality**

| Study | Design/population | Smoking definition | Findings (all comparisons are vs. never unless otherwise specified) | Comments |
|---|---|---|---|---|
| **A) Cancer-related mortality** | | | | |
| Thrasher et al. 1994 | • 531 transitional cell cancer patients | Ever/never | • p = 0.85 | 1969–1990; chart review; smoking not clearly defined; patients treated with radical cystectomy |
| Fujusawa et al., 1999 | • 369 Stage I NSCLC patients | Pack-years | • ≥30 Pack-years: 1.39 (0.66–2.91) | 1981–93. Patients treated with surgery |
| Manjer et al. 2000a | • 792 breast cancer patient | C/F/N | • Former: 1.62 (0.51–5.07)<br>• Current: 3.31 (1.57–6.95) | 1977–1986; chart review; Malmo Mammographic Screening Trial |
| Browman et al. 2002 | • 148 Stage III–IV head/neck cancer patients | Current/noncurrent recent quitters | • 1.23 (p = 0.056) | Referent is quitters who stopped smoking within 12 weeks prior to RT; patients treated with RT |
| Frank et al. 2002 | • 1,801 clear cell renal cell carcinoma patients | Ever/never | • 1.07 (0.91–1.26) | 1970–1998; patients treated with surgery |
| Gorsky et al. 2004 | • 322 patients with tongue cancer | Smoker/nonsmoker | • Reported as not statistically significant in the text. (p. 549) | 1979–1994;chart review; smoking not clearly defined |
| Pickles et al. 2004 | • 601 prostate cancer patients | Current/noncurrent | • 2.89 (p = 0.08) | 1994–1997; patients treated with external beam RT |
| Kawai et al. 2005 | • 3082 Stage IA NSCLC patients | Pack-years | • <40 Pack-years: 1.0<br>• 40+ Pack-years: 1.22 (0.98–1.51) | 1982–97. Disease specific survival. Chart review. Patients treated with surgery |
| Wright et al. 2005 | • 255 IB–IIB cervical cancer patients | Current/noncurrent | • 4.06 (1.15–14.38) | |
| Kjaerbye-Thygesen et al. 2006 | • 295 Stage III ovarian cancer patients | C/F/N | • Former: 0.93 (0.67–1.30)<br>• Current: 1.65 (1.22–2.24) | 1994–1999; Danish Malignant Ovarian Cancer Study |
| Merrick et al. 2006 | • 938 consecutive T1b–T3a prostate cancer patients | C/F/N | • Former: p = 0.19<br>• Current: p = 0.48 | 1995–2002; patients treated with brachytherapy +/- androgen deprivation therapy |
| Modesitt et al. 2006 | • 3,562 endometrial cancer patients | Current/notcurrent | • 1.38 (1.09–1.75) | 1995–2002 |

**Table 6.30*S* Continued**

| Study | Design/population | Smoking definition | Findings (all comparisons are vs. never unless otherwise specified) | Comments |
|---|---|---|---|---|
| Munro et al. 2006 | • 284 CRC patients | Current/Noncurrent | • 2.55 (1.40–4.64) | 1997–1999; current defined as active smoking at first postoperative visit; patients treated with curative surgery |
| Nagle et al. 2006 | • 676 primary epithelial ovarian cancer cases | C/F/N | • Former: 1.09 (0.86–1.39)<br>• Current: 1.36 (1.01–1.84) | 1990–1993 |
| Williams et al. 2006 | • 1073 Stage I–IIIB NSCLC patients treated with curative surgery | Pack-years | • <30 : 1.0 (referent)<br>• 30-50: 1.12 (0.81–1.54)<br>• 50-75: 1.38 (1.01–1.90)<br>• >75: 1.19 (0.86–1.65)<br>• Smoking at diagnosis: 0.95 (0.73–1.24) | 1997–2001. Post-recurrence mortality. Patients treated with curative surgery. Referent group includes patients with <30 Pack-years history |
| Chia et al. 2007 | • 745 endometrial cancer patients | C/F/N | • Former: 1.4 (0.7–2.9)<br>• Current: 0.5 (0.1–2.1) | 1991–1994; structured health behavior assessment |
| Giovannucci et al. 2007 | • 3,544 prostate cancer patients | Ever/Never | • 1.41 (1.04–1.91) | Health Professional Follow-Up Study; questionnaire every 2 years |
| Holmes et al. 2007 | • 5,056 breast cancer patients | C/F/N | • Former: 0.93 (0.79–1.10)<br>• Current: 1.00 (0.83–1.19) | Breast cancer mortality; Nurse's Health Study; repeated structured questionnaires |
| Hung JJ et al. 2007 | • 445 Stage I NSCLC patients with tumors 3 cm or less | Pack-years | • 1.011 (1.004–1.018) | 1980–2000; chart review; pack-years analyzed as continuous variable |
| Odongua et al. 2007 | • Cervical cancer patients from 475,398 women in screening program | C/F/N | • Former: 1.31 (0.68–2.52)<br>• Current: 2.00 (1.23–2.91) | 1992 |
| Sagiv et al. 2007 | • 1,273 breast cancer patients | C/F/N | • Obese<br>– Former: 0.91 (0.40–2.07)<br>– Current: 1.97 (0.89–4.36)<br>• Overweight<br>– Former: 0.66 (0.29–1.54)<br>– Current: 0.84 (0.31–2.29)<br>• Normal weight<br>– Former: 1.07 (0.53–2.16)<br>– Current: 0.80 (0.35–1.79) | 1996–1997 Long Island Breast Cancer Study; Questionnaire following breast cancer diagnosis |
| Bittner et al. 2008 | • 1,354 prostate cancer patients | C/F/N | • Reported as not statistically significant in the text. (p. 437) | 1993–2004; patients treated with brachytherapy +/- androgen deprivation +/- external beam RT |

**Table 6.30*S* Continued**

| Study | Design/population | Smoking definition | Findings (all comparisons are vs. never unless otherwise specified) | Comments |
|---|---|---|---|---|
| Dal Maso et al. 2008 | • 1,453 breast cancer patients | C/F/N | • Former: 1.27 (0.97–1.67)<br>• Current <15 cpd: 1.39 (1.02–1.90)<br>• Current ≥15 cpd: 1.23 (0.82–1.83) | 1991–1994; structured questionnaire 1 year prior to diagnosis |
| Gong et al. 2008 | • 752 prostate cancer patients | C/F/N | • Former ≥10 years: 0.45 (0.19–1.05)<br>• Former <10 years: 1.48 (0.50–4.37)<br>• Current: 2.66 (1.10–6.43) | 1993–1996; cases from case-control study; structured interview |
| Parker et al. 2008 | • 2,242 renal cell carcinoma patients | C/F/N | • Current: 0.93 (0.77–1.12) | 1970–2002; patients treated with surgery. |
| Perng et al. 2008 | • 299 stage IIIB–IV NSCLC | Ever/Never | • 1.52 (1.18–1.94) | 2005–2006; patients who failed chemotherapy and treated with erlotinib |
| Toyooka et al. 2008 | • 408 advanced or recurrent NSCLC patients | Ever/Never | • ≥20 pack-years: 1.0 (referent)<br>• <20 pack-years: 1.0 (0.74–1.61)<br>• Never: 0.76 (0.54–1.07) | Chart review; analyses based upon pack year |
| Yang et al. 2008 | • 635 ovarian cancer patients responding to follow-up questionnaire | C/F/N | • Former: 0.91 (0.69–1.25)<br>• Current: 0.94 (0.70–1.26) | 1994–1995; follow-up questionnaire only answered by surviving patients |
| Coker et al. 2009 | • 2,661 women with cervical cancer | Current/Not current | • 1.21 (1.01–1.46) | 1995–2005 |
| Hotta et al. 2009 | • 365 NSCLC patients | Per pack year | • Males: 0.97 (0.95–1.00)<br>• Females: 1.00 (0.96–1.04) | 2000–2003; cancer related mortality; risks stated per pack year; patients treated with gefitinib |
| Marks et al. 2009 | • 2,818 HLA identical sibling or matched unrelated donor allogeneic transplants for CML | Ever (High dose, low dose)/Never | • HLA-identical sibling donor group<br>– Low dose: 1.14 (0.95–1.37)<br>– High dose: 1.52 (1.14–2.04)<br>• Unrelated donor group<br>– Ever: 0.97 (0.76–1.25) | 1990–2004 |
| Nose et al. 2009 | • 477 NSCLC patients tested for EGFR mutation | Ever/Never | • 2.0 (0.86–4.76) | 1993–2007 |
| Tiseo et al. 2009 | • 651 stage IIIB–IV NSCLC | Ever/Never | • 1.71 ($p<0.001$) | Patients treated with gefitinib |
| Watters et al. 2009 | • 16,640 prostate cancer patients | C/F/N | • Former: 1.03 (0.83–1.27)<br>• Current: 1.69 (1.25–2.27) | 1995–1996; NIH-AARP Diet and Health Study |

**Table 6.30*S* Continued**

| Study | Design/population | Smoking definition | Findings (all comparisons are vs. never unless otherwise specified) | Comments |
|---|---|---|---|---|
| Kim et al. 2010 | • 342 NSCLC patients | Ever/Never | • 1.15 (0.82–1.62) | 2006–8; chart review; patients treated with erlotinib or gefitinib |
| Nugent et al. 2010 | • 111 stage IB2-IV cervical cancer patients | Ever/Never | • Reported as not statistically significant in the text. (p. 440) | 2003–2007; chart review; patients treated with RT + chemotherapy |
| Sardari et al. 2010 | • 239 NSCLC patients | Current/Noncurrent | • 1.62 (1.08–2.41) | 1991–2001; patients treated with surgery |
| Weinmann et al. 2010 | • 768 prostate cancer patients matched to 929 non-cancer controls | C/F/N | • Former: 1.0 (0.81–1.3)<br>• Current: 1.5 (1.1–2.0) | 1997–2001 |
| Farshadpour et al. 2011 | • 2,012 head/neck cancer patients | Current/Noncurrent | • 1.26 (0.86–1.85) | 1980–2004; smoking combined with drinking in analysis |
| Kenfield et al. 2011 | • 5,366 prostate cancer patients | C/F/N | • Former: 1.05 (0.86–1.27)<br>• Current: 1.61 (1.11–2.32) | Health Professionals Follow-Up Study; questionnaire every 2 years |
| Kountourakis et al. 2011 | • 49 patients with T2 esophageal cancer | Smoker/Nonsmoker | • 4.82 (1.38–16.81) | 1997–2009; patients treated with surgery, RT, and chemotherapy |
| Maeda et al. 2011a | • 1,870 stage I–II NSCLC patients | Ever/Never | • ($p<0.001$) | 1992–2007; chart review; patients treated with curative surgery |
| Ngô et al. 2011 | • 257 patients with cervical cancer < 4 cm in diameter | Current smokers >10 cpd vs. ≤10 cpd | • 2.63 (1.30–5.34) | 1985–2008; referent category includes light current + former + never smokers; patients treated with preoperative brachytherapy and surgery. 5-year mortality |
| Phipps et al. 2011 | • 2,264 colorectal cancer patients | C/F/N | • Former: 1.14 (0.93–1.38)<br>• Current: 1.30 (1.09–1.74) | 1998–2007; structured questionnaire post-diagnosis |
| Richards et al. 2011 | • 423 Stage I–III CRC patients | C/F/N | • 1.25 (1.02–1.53) univariate, $p = 0.09$ multivariate | 1997–2007; smoking not clearly defined, likely current; patients treated with curative surgery |
| Shiono et al. 2011 | • 201 stage I NSCLC patients | Ever/Never | • 1.3 (0.04–43.3) | 2004–2008; chart review; smoking not clearly defined; patients treated with surgery |
| Yafi et al. 2011 | • 2,287 bladder cancer cases | Smoker/Nonsmoker | • 1.30 (1.005–1.69) | 1998–2008; chart review; treated with radical cystectomy |
| Bostrom et al. 2012 | • 564 bladder cancer patients | Ever/Never | • Men: 1.7 (1.1–2.5)<br>• Women: 1.2 (0.7–2.1) | 1991–2008; chart review; treated with radical cystectomy |

**Table 6.30*S* Continued**

| Study | Design/population | Smoking definition | Findings (all comparisons are vs. never unless otherwise specified) | Comments |
|---|---|---|---|---|
| Gillison et al. 2012 | • 502 stage III–IV head/neck cancer patients | Current/Noncurrent | • RT: 2.19 (1.48–3.25)<br>• RT+CT: 2.73 (1.37–5.45) | Data from RTOG 9003 + RTOG 0129, phase III trials treating with RT +/- chemotherapy |
| Gridelli et al. 2012 | • 780 stage IIIB–IV NSCLC patients | Ever/Never | • 1.24 (1.04–1.48) | Patients treated on randomized TORCH trial |
| Haughey et al. 2012 | • 211 p16+ oropharyngeal cancer patients | C/F/N | • Disease free mortality<br>– Current: 5.25 (1.39–19.85)<br>• Disease specific mortality<br>– Current: 5.36 (0.55–51.53) | 1996–2010; patients treated with laser microdissection |
| Kawakita et al. 2012 | • 222 patients with oral cavity cancer | Current/Noncurrent | • 2.08 (1.04–4.15) | 2001–2005; disease free mortality; referent category is light smokers |
| Kroeger et al. 2012 | • 802 renal cell carcinoma patients | Ever/Never | • 1.35 (1.09–1.67) | 1989–2007; chart review |
| Lee et al. 2012b | • 670 stage IIIB–IV NSCLC patients | C/F/N | • Former: 1.02 (0.79–1.32)<br>• Current: 1.61 (0.91–2.86) | Patients treated with erlotinib on TOPICAL trial |
| Lee et al. 2012a | • 924 stage IIIB–IV NSCLC patients | Ever/Never | • Not significant (Forest plot) | 2006–2008; patients enrolled on phase III ZEPHYR trial in patients who failed EGFR therapy |
| Wang et al. 2012 | • 301 stage II–IIIA NSCLC patients | Ever/Never | • 0.97 (0.72–1.29) | 2000–2006; chart review; patients treated with surgery |
| Chang et al. 2013 | • 245 stage IIIB–IV NSCLC patients | Ever/Never | • 1.20 (0.80–1.82) | 2002–2011; patients treated with chemotherapy |
| Warren et al. 2013 | • 5,185 cancer patients with 13 types of malignancy. | Current/Recent quit/ Former/Never | • Current vs. former: 1.23 (1.09–1.39)<br>• Current vs. recent quit: 1.08 (0.94–1.25)<br>• Current vs. never: 1.18 (1.03–1.36) | 1982–1998; structured tobacco assessment; current smoking vs. variable referent categories |
| **B) Cancer-related survival** | | | | |
| Chelghoum et al. 2002 | • 642 AML patients | Ever/Never | • Pack-years<br>– 0-20: 12.6 months<br>– ≥20: 9.1 month (NS)<br>• Duration smoked (years)<br>– 0–30: 12.6 months<br>– ≥30: 8.2 months (p = 0.03) | 1984–1998; median survival; structured tobacco assessments by patients or relatives |

**Table 6.30*S* Continued**

| Study | Design/population | Smoking definition | Findings (all comparisons are vs. never unless otherwise specified) | Comments |
|---|---|---|---|---|
| Videtic et al. 2003 | • 186 limited stage SCLC | Current, non-current | • Current: 15.8 mo<br>• Non-current: 14.8 mo (not significant) | 1989–99. Disease free survival. Chart review. Patients treated with chemoradiotherapy |
| Wu et al. 2003 | • 321 Stage I NSCLC patients | Pack-years | • 20 or less: 63.6%<br>• >20: 49.5% (p<0.002) | 1980–90. 10 year cancer related survival. Chart review. Patients treated with surgery |
| Fox et al. 2004 | • 237 Stage I–III NSCLC patients | Current, non-current | • Stage I–II<br>– Current: 25.3 mo<br>– Non-current: 28.1 mo (p=0.32)<br>• Stage III<br>– Current: 20.3 mo<br>– Non-current: 18.9 mo (p=0.65) | 1991–2001. Median cancer specific survival. Chart review. Current smoking include patients who quit within 12 months of RT. Patients treated with RT |
| Iizasa et al. 2004 | • 402 Stage I lung cancer patients | Pack-years | • Cancer specific survival<br>– 30+: 70.7%<br>– <30: 79.3% (p=0.46)<br>• Non-cancer specific survival<br>– 30+: 67.7%<br>– <30: 94.3% (p<0.0001) | 1985–97. 10 year survival. Patients treated with surgery |
| Yamamoto et al. 2004 | • 207 Stage I–IIIA NSCLC | Smoking habit | • Yes: 69.9%<br>• No: 63.4% (not significant) | 1990–5. Disease free survival. Smoking not clearly defined. Chart review |
| Guntinas-Lichius et al. 2006 | • 69 patients with unknown primary of the head/neck | Smoker/Nonsmoker | • Reported as not statistically significant in the text | 1987–2002; 5-year survival; chart review; smoking not clearly defined |
| Lee et al. 2006 | • 575 stage IIIB–IV NSCLC patients | Ever/Never | • Progression free survival<br>– Never: 3.7 mo<br>– Ever: 1.7 mo (p<0.001) | 2002–5. Median progression free survival. Chart review. Patients treated with gefitinib |
| Pine et al. 2007 | • 731 Stage I-IV NSCLC patients | Pack-years | • White: 1.00 (0.99–1.00)<br>• African American: 1.00 (0.99–1.01) | 1998–2004. Pack-years analyzed as continuous variable |
| Hanagiri et al. 2008 | • 770 stage I–IV NSCLC | Ever/Never | • Never: 70.2%<br>• 20 Pack-years or less: 69.6%<br>• >20 Pack-years: 67.3% (not significant) | 1994–1995; chart review; patients treated with surgery |
| Sakao et al. 2008 | • 121 NSCLC patients with tumors <2 cm | Ever/Never | • Ever: 80.4%<br>• Never: 98.0% (p = 0.03) | 1996–2006; chart review; patients treated with surgery |
| Bostrom et al. 2009 | • 248 bladder cancer patients | Ever/Never | • 0.88 (p=0.055) | 1986–2005; chart review; patients treated with radical cystectomy |

**Table 6.30*S* Continued**

| Study | Design/population | Smoking definition | Findings (all comparisons are vs. never unless otherwise specified) | Comments |
|---|---|---|---|---|
| Chang et al. 2010 | • 110 NSCLC patients | Ever/Never | • Ever: 2.07 months<br>• Never: 3.22 (p = 0.116) | 2006–2008; median survival chart review |
| Chen et al. 2011a | • 202 head/neck cancer patients | Current/Noncurrent | • 0.65 (p = 0.01) | 1998–2008; chart review; patients treated with RT +/- surgery |
| Junor et al. 2012 | • 254 head/neck cancer patients | C/F/N | • Current: 55.8%<br>• Former: 67.2%<br>• Never: 82.0% (p = 0.045) | 5-year cancer related survival |

*Note:* **Cancer related mortality** = disease specific, disease free, cancer specific mortality or survival; **chart review** = tobacco information collected by chart review or where tobacco collection information is not clearly defined; **NMIBC =** nonmuscle invasive bladder cancer.

**Table 6.31*S* Associations between smoking and developing a second primary cancer in cancer patients**

| Study | Design/population | Smoking definition | Findings (all comparisons are vs. never unless otherwise specified) | Comments |
|---|---|---|---|---|
| Hiyama et al. 1992 | • 472 male laryngeal cancer patients | Current cpd | • 1–19: 2.0 (p <0.01)<br>• 20–39: 2.2 (p <0.01)<br>• ≥40: 2.5 (p <0.01) | 1965Ð1975; observed/expected; chart review |
| Kaldor et al. 1992 | • 98 HD patients with subsequent lung cancer matched to 259 HD controls | Ever/never | • 13.0 (3.0–59) | Lung cancer; chart review |
| Richardson et al, 1993 | • 540 SCLC patients | Current smokers compared to general population | • General population: 1.0 (referent)<br>• Continue after diagnosis: 32 (12–69)<br>• Quit after diagnosis: 11 (4.4–23) | 1973–1989; patients enrolled on clinical trials through National Cancer Institute |
| van Leeuwen et al. 1995 | • 30 HD patients with subsequent lung cancer matched to 82 HD controls | Current/noncurrent | • <1: 1.0 (referent)<br>• 1–10: 2.9 (1.1–8.0)<br>• >10: 6.2 (1.2–3.1) | 1966–1986; lung cancer; chart review; current defined as smoking after diagnosis (pack-years) |
| Barbone et al. 1996 | • 380 head/neck cancer patients | Smoking history | • All:<br>– Never or very light: 1.0 (referent)<br>– Light: 1.5 (0.5–4.9)<br>– Intermediate: 2.7 (0.5–13.4)<br>– Heavy: 4.3 (0.7–26.9)<br>• Head and neck<br>– Never or very light: 1.0 (referent)<br>– Light: 2.3 (0.4–12.2)<br>– Intermediate: 2.7 (0.5–13.4)<br>– Heavy: 4.3 (0.7–26.9) | 1984–1991; referent category included very light or never |
| Tucker et al. 1997 | • 611 2-year survivors of SCLC | Current smokers compared to general population | • General population: 1.0 (referent)<br>• Continued after diagnosis: 17 (11–16)<br>• Quit at diagnosis: 9.9 (5.3–17)<br>• Quit prior to diagnosis: 9.4 (4.7–17) | Chart review; Lung Cancer Working Cadre |
| Kawahara et al. 1998 | • 980 SCLC patients | Current smokers compared to general population | • General population: 1.0 (referent)<br>• Continue after diagnosis: 5.4 (2.7–9.6)<br>• Quit after diagnosis: 1.6 (0.3–4.6) | 1978–1992. Chart review; analysis in 70 patients with at least 2 years of survival |
| Kinoshita et al. 2000 | • 1,614 stage I-III gastric cancer patients | C/F/N | • Former: 0.95 (0.42–2.13)<br>• Current: 1.82 (1.02–3.26) | 1978–1992; second primary; chart review |
| Obedian et al. 2000 | • 1,029 early stage breast cancer patients | C/F/N | • Never: 1.0 (referent)<br>• Former: 7.01<br>• Current: 8.96 (p = 0.06) | 1970–1990; lung cancer incidence at 14.6 years; chart review; patients treated with surgery + RT |

**Table 6.31*S* Continued**

| Study | Design/population | Smoking definition | Findings (all comparisons are vs. never unless otherwise specified) | Comments |
|---|---|---|---|---|
| Kokawa et al. 2001 | • 368 resected superficial esophageal cancers | Brinkman Index | • 1000+: 1.70 (p = 0.006) | 1966–1998; second primary; referent group includes smokers and nonsmokers |
| Lippman et al. 2001 | • 1166 T1-3 NSCLC patients | C/F/N | • Former: 3.10 (0.75–12.84)<br>• Current: 2.72 (0.64–11.51) | Randomized trial |
| Travis et al. 2002 | • 222 HD patients with lung cancer and 444 matched controls | Heavy/nonheavy | • Nonheavy:<br>– RT-, chemotherapy-: 1.0 (referent)<br>– RT+, chemotherapy-: 7.2 (2.9–21.2)<br>– RT-, chemotherapy+: 4.3 (1.8–11.7)<br>– RT+, chemotherapy+: 7.2 (2.8–21.6)<br>• Heavy:<br>– RT-, chemotherapy-: 6.0 (1.9–20.4)<br>– RT+, chemotherapy-: 20.2 (6.8–68)<br>– RT-, chemotherapy+: 16.8 (6.2–53)<br>– RT+, chemotherapy+: 49.1 (15.1–187) | Lung cancer; chart review; nonheavy includes <1 PPD, former, and never |
| Ford et al. 2003 | • 280 breast cancer patients with subsequent primary lung cancer matched to 300 breast cancer patients without lung cancer | C/F/N | • All:<br>– Former: 3.68 (2.09–6.48)<br>– Current: 12.90 (8.17–20.37)<br>• Smoking and RT treatment<br>– Noncurrent, No RT: 1.0 (referent)<br>– Noncurrent, Yes RT: 0.54 (0.26–1.13)<br>– Current, No RT: 6.00 (3.55–10.13)<br>– Current, Yes RT: 9.00 (5.08–15.9) | 1960–1997; lung cancer following breast cancer; chart review |
| Franchin et al. 2003 | • 410 T1-T2 laryngeal cancer patients | Current/noncurrent | • 2.07 (calculated from data in text p. 769) | Chart review; no statistical testing |
| Gilbert et al. 2003 | • HD patients: 199 with subsequent lung cancer matched with 393 without lung cancer | C/F/N | • Former: 6.8 (2.8–19.5)<br>• Current: 24.0 (10.3–68) | 1965–1994; lung cancer; chart review; all patients treated with RT |
| Matsubara et al. 2003 | • 679 squamous cell esophageal cancer patients | Smoking habit | • 2.92 (p=0.02) | 1989–2001; chart review; smoking not clearly defined |
| Kim et al. 2004 | • 342 Stage I-IV NSCLC patients treated with surgery | Current, noncurrent | • 2.32 (1.28–8.97) | 1994–1999; chart review |

**Table 6.31*S* Continued**

| Study | Design/population | Smoking definition | Findings (all comparisons are vs. never unless otherwise specified) | Comments |
|---|---|---|---|---|
| Dikshit et al. 2005b | • 876 male laryngeal or hypopharyngeal cancer patients | Pack-years | • All:<br>– 0–20: 1.0 (referent)<br>– 21–40: 1.3 (0.8–2.3)<br>– 41–60: 0.9 (0.5–1.7)<br>– >60: 1.6 (0.8–3.0)<br>• Lung:<br>– 0–20: 1.0 (referent)<br>– 21–40: 3.3 (0.9–11.0)<br>– 41–60: 2.4 (0.7–8.6)<br>– >60: 3.9 (1.0–14.6) | Structured interviews; referent category included never smokers plus smokers of up to 20 pack-years |
| Lin et al. 2005 | • 1,257 head/neck cancer patients | Ever/never | • 5.2 (1.3–22) | 1984–1998; smoking not clearly defined (implied as ever) |
| Prochazka et al. 2005 | • 182 breast cancer patients with subsequent lung cancer | Ever/never | • 2.09 (p <0.001) | 1958–2000; relative risk of lung cancer in smokers vs. nonsmokers who received RT; chart review |
| Khuri et al. 2006 | • 1,190 Stage I-II head/neck cancer patients | C/F/N | • Former: 1.63 (0.94–2.83)<br>• Current: 2.20 (1.28–3.78) | Smoking-related second primary; patients treated with surgery +/- RT; Phase III trial of isotretinoin |
| Moser et al. 2006 | • 748 aggressive NHL patients | Ever/never | • 2.11 (1.33–4.11) | 1980–1999; second primary; patients enrolled in 1 of 4 European Organisation for Research and Treatment of Cancer trials |
| Boorjian et al. 2007 | • 9,780 prostate cancer patients | Current/noncurrent | • No RT (all): 1.0 (referent)<br>• Yes RT (all): 1.59 (0.97–2.6)<br>• Current (all): 2.08 (1.09–3.97)<br>• Current + RT: 3.65 (1.45–9.16) | Bladder cancer; CaPSURE study |
| Park et al. 2007 | • 14,181 male cancer patients including 204 patients with second primary cancer | C/F/N | • All:<br>– Former: 0.87 (0.56–1.35)<br>– Current: 1.13 (0.77–1.67)<br>• Smoking related:<br>– Former: 1.03 (0.46–2.31)<br>– Current: 2.02 (1.02–4.03) | 1996–2002; patients part of National Health Insurance Corporation Study |
| van den Belt-Dusebout et al. 2007 | • 2,707 testicular cancer patients with at least 5 years of survival | Current/noncurrent | • 1.8 (1.3–2.4) | 1965–1995; second primary; chart review; current = smoking at or following diagnosis; Netherlands Testicular Cancer Survivors Study |

**Table 6.31*S* Continued**

| Study | Design/population | Smoking definition | Findings (all comparisons are vs. never unless otherwise specified) | Comments |
|---|---|---|---|---|
| Kaufman et al. 2008 | • 114 breast cancer patients with primary lung cancer 10+ years after diagnosis matched to 380 breast cancer controls without lung cancer | Ever/never | • No RT:<br>– Never: 1.0 (referent)<br>– Ever: 12.7 (2.8–57.3)<br>• Patients treated with RT:<br>– Never: 1.9 (0.3–14.0)<br>– Ever: 32.5 (6.6–160.3) | 1965–1989; lung cancer following breast cancer |
| Rossini et al. 2008 | • 326 head/neck cancer patients | Smoking | • None: 0%<br>• Ethanol only: 20%<br>• Tobacco only: 0%<br>• Both: 14.3% ($p < 0.05$) | 1995–2000; esophageal cancer risk; chart review; smoking combined with ethanol in analysis |
| Sanchez et al. 2008 | • Breast cancer patients: 267 with second nonbreast primary cancer vs. 465 without second primary | Smoker/nonsmoker | • 3.16 (1.23–9.15) | 1975–2003; second primary; chart review |
| Knight et al. 2009 | • 708 asynchronous contralateral breast cancer vs. 1,399 unilateral breast cancer patients | C/F/N | • Ever: 1.1 (0.9–1.6)<br>• Ever after diagnosis: 1.2 (0.9–1.5) | 1985–2001; contralateral breast cancer; structured interview; includes patients treated +/- RT |
| Leon et al. 2009 | • 514 case control study in head/neck cancer patients | Current cpd | • 0: 1.0 (referent)<br>• 1–10: 0.7 (0.2–1.1)<br>• 11–20: 2.8 (1.2–7.1)<br>• >20: 10.9 (2.1–55.4) | Chart review; current defined as tobacco use after diagnosis; referent group includes former tobacco use |
| Li et al. 2009a | • 365 patients with ER+ breast cancer and contralateral second breast cancer compared with 726 patients with ER+ breast cancer and no contralateral cancer | C/F/N | • At diagnosis:<br>– Former: 1.2 (0.8–1.7)<br>– Current: 1.8 (1.1–3.2)<br>• At most recent follow-up:<br>– Former: 1.2 (0.8–1.7)<br>– Current: 2.2 (1.2–4.0) | 1990–2007; contralateral breast cancer; structured interview |
| Farshadpour et al. 2011 | • 2,012 head/neck cancer patients | Current/noncurrent | • 1.34 (0.96–1.88) | 1980–2004; second primary tumor mortality; smoking combined with drinking in analysis |
| Peck et al. 2012 | • 356 oropharyngeal cancer patients | Ever/never | • HPV-, never: 17.6%<br>• HPV-, ever: 13.2%<br>• HPV+, never: 0%HPV+, ever: 10.5% | 1995–2004; 5-year second primary rate in HPV seropositive patients |

*Note*: **C/F/N** = current/former/never; **CaPSURE** = Cancer of the Prostate Strategic Urologic Research Endeavor; **cpd** = cigarettes per day; **CT** = chemotherapy; **ER** = estrogen receptor; **HD** = Hodgkin's disease; **NSCLS** = non-small-cell lung cancer; **pack-years** = the number of years of smoking multiplied by the number of packs of cigarettes smoked per day; **RT** = radiotherapy.

**Table 6.32*S* Associations between smoking and cancer recurrence**

| Study | Design/population | Smoking definition | Findings (all comparisons are vs. never unless otherwise specified) | Comments |
|---|---|---|---|---|
| Scanlon et al. 1995 | • 835 breast cancer patients | Packs smoked | • 0: 1.0 (referent)<br>• <10,000: 1.06 (0.51–2.20)<br>• 10,001–20,000: 3.10 (1.54–6.25)<br>• >20,000: 3.73 (1.58–8.92) | 1982–1991; lung metastases after diagnosis; current included smoking within 2 years of diagnosis |
| Fleshner et al. 1999 | • 286 superficial transitional cell (NMIBC) cancer patients | Current/noncurrent | • 1.40 (1.03–1.91) | 1985–1995; chart review |
| Lippman et al. 2001 | • 1166 T1-3 NSCLC patients | C/F/N | • Former: 0.87 (0.46–1.67)<br>• Current: 0.73 (0.37–1.44) | Recurrence; randomized trial |
| Leibovich et al. 2003 | • 1,671 clear cell renal cell carcinoma patients | Ever/never | • 1.02 (0.85–1.22) | 1970–2000; progression to metastases; patients treated with surgery |
| Muscat et al. 2003 | • 244 breast cancer patients | Current/noncurrent | • 2.1 (0.9–5.1) | 1994–1996 |
| Yokoyama et al. 2003 | • 185 women with CIN I-II | C/F/N | • Former: 2.75 (0.79–9.58)<br>• Current: 1.42 (0.46–4.42) | 1995–1996; progression |
| Chang et al. 2004a | • 114 CML patients | Pack-years | • 1.7% per pack-year (p = 0.01) | 1997–2001; patients treated with hematopoietic stem cell transplant; 1-year mortality |
| Oefelein et al. 2004 | • 222 advanced prostate cancer including 133 hormone refractory patients | C/F/N | • Never: 35 months<br>• Former: 23 months<br>• Current: 12 months (p = 0.00001) | 1987–2003; median progression to hormone refractory disease; chart review |
| Pickles et al. 2004 | • 601 prostate cancer patients | Current/noncurrent | • 1.68 (1.11–2.56) | 1994–1997; patients treated with external beam RT |
| Brumund et al. 2005 | • 270 patients with T1-T3 true vocal cord cancer | Pack-years | • Reported as not significant in text (p. 319) | 1975–2000; chart review |
| Leibovici et al. 2005 | • 465 Caucasian bladder cancer patients (MIBC + NMIBC) matched to 450 controls | C/F/N | • Recurrence in NMIBC<br>– Former: 1.11 (0.73–1.70)<br>– Current: 0.81 (0.47–1.37)<br>• Progression in NMIBC<br>– Former: 1.30 (0.53–3.16)<br>– Current: 0.59 (0.17–2.03) | 1995–2003; current include patients who quit in 12 months prior to diagnosis |

**Table 6.32*S* Continued**

| Study | Design/population | Smoking definition | Findings (all comparisons are vs. never unless otherwise specified) | Comments |
|---|---|---|---|---|
| Sardari et al. 2005 | • 321 Stage I-IIIB NSCLC patients | C/F/N | • Current: 1.0 (referent)<br>• Recent quitters: 0.54 (0.30–1.00)<br>• Former: 0.53 (0.34–0.84)<br>• Never: 0.66 (0.34–1.27) | 1991–2001; recurrence and metastasis; patients treated with surgery. detailed smoking information.;recent quit within 3 months |
| Donat et al. 2006 | • 1,159 renal cell carcinoma patients | Ever/never | • 1.10 (0.73–1.67) | 1995–2003; progression; patients treated with surgery |
| Heist et al. 2006 | • 382 Stage I NSCLC patients | C/F/N, pack-years | • Former: 1.25 (0.72-2.18)<br>• Current: 1.49 (0.84-2.61)<br>• Pack-years: 1.005 (1.002-1.008) | 1992–2001; recurrence; pack-years analyzed as continuous variable; patients treated with surgery |
| Khuri et al. 2006 | • 1,190 Stage I-II head/neck cancer patients | C/F/N | • Current vs. former: 1.12 (0.76–1.65)<br>• Current vs. never: 1.37 (0.76–2.46) | Patients treated with surgery +/- RT; randomized phase III trial of isotretinoin vs. placebo |
| Merrick et al. 2006 | • 938 consecutive T1b-T3a prostate cancer patients | C/F/N | • Former: 0.952 (0.434)<br>• Current: 2.101 (0.038) | 1995–2002; patients treated with brachytherapy +/- androgen deprivation therapy |
| Waggoner et al. 2006 | • 315 advanced cervical cancer patients | Current/noncurrent | • Unadjusted: 1.45 (1.05–1.99)<br>• Adjusted: 1.35 (0.93–1.94) | Progression; GOG 165 trial |
| Zhou et al. 2006 | • 543 Stage I-IIB NSCLC patients | C/F/N | • Current: 1.0 (referent)<br>• Former:<br>– Quit 1–8 years: 0.76 (0.56–1.03)<br>– Quit 9–17 years: 0.69 (0.50–0.95)<br>– Quit 18+ years: 0.68 (0.49–0.96)<br>• Never: 0.55 (0.31–0.97) | 1992–2002; recurrence free survival; current smoking is referent group |
| Chen et al. 2007a | • 265 men with NMIBC | Current, quitter, former, never | • Quitting: 1.0 (referent)<br>• Never: 2.2 (1.1–4.5)<br>• Former: 1.4 (0.7–2.7)<br>• Current: 2.2 (1.2–4.0) | 1997–2005; referent category is quitting smoking between 1 year prior and 3 months after diagnosis |
| Gillespie et al. 2007 | • 325 head/neck cancer patients | Smoker/nonsmoker | • 1.22 (0.58–2.55) | Chart review; case control study for COX2 inhibitors; smoking not clearly defined |
| Kim et al. 2007 | • 106 recurrent head/neck cancer patients | C/F/N | • Current: 95%<br>• Former: 71%<br>• Never: 67% (p = 0.02) | 1996–2006; recurrence after salvage surgery; chart review; patients treated with salvage surgery and reconstruction |
| Mai et al. 2007 | • 68 anal cancer patients | Current/noncurrent | • 2.75 (0.55–13.64) | 1990–2006; chart review; patients treated with RT + chemotherapy |

**Table 6.32*S* Continued**

| Study | Design/population | Smoking definition | Findings (all comparisons are vs. never unless otherwise specified) | Comments |
|---|---|---|---|---|
| Pantarotto et al. 2007 | • 416 prostate cancer patients | C/F/N | • Former: 2.90 (p = 0.03)<br>• Current: 5.24 (p = 0.003) | 1990–1999; distant failure; patients treated with external beam RT; chart review |
| Ritoe et al. 2007 | • 402 laryngeal cancer patients | Current/noncurrent | • 1.46 (0.93–2.29) | 1990–1995; chart review; current = continued smoking after treatment |
| Duffy et al. 2008 | • 444 head/neck cancer patients | C/F/N | • Former: 1.15 (0.66–2.02)<br>• Current: 1.39 (0.76–2.53) | 2003–2007; structured health assessment |
| Meyer et al. 2008 | • 540 head/neck cancer patients | Current/noncurrent | • 2.41 (1.25–4.64) (β-carotene treated pts.) | 1994–2000; patients treated with RT, randomized to β-carotene |
| Rades et al. 2008 | • 181 nonmetastatic lung cancer patients | Current/noncurrent | • 1.74 (1.06–2.89) | 2000–2005; chart review; patients treated with RT |
| Ramamoorthy et al. 2008 | • 64 anal cancer patients | Smoker/nonsmoker | • 1.43 (p = 0.17) | 1999–2005; smoking within 5 years of treatment; chart review |
| Guo et al. 2009 | • 327 stage I-III NSCLC patients | Current/noncurrent | • 0: 1.0 (referent)<br>• 10 cigarettes/day: 1.12 (1.1204–1.1217)<br>• 20 cigarettes/day: 1.2567 (1.2559–1.2575)<br>• 40 cigarettes/day: 1.5793 (1.5783–1.5802) | Patients pooled from 4 lung cancer cohorts |
| Marks et al. 2009 | • 2,818 HLA identical sibling or matched unrelated donor allogeneic transplants for CML | Ever (high dose, low dose)/never | • HLA-identical sibling donor group<br>– Low dose: 1.75 (1.23–2.49)<br>– High dose: 1.02 (0.44–2.36)<br>• Unrelated donor group<br>– Ever: 0.67 (0.0.28–1.56) | 1990–2004 |
| Sandoval et al. 2009 | • 146 oral cavity cancer patients | C/F/N | • Current: 1.0 (referent)<br>• Former: 0.75 (0.34–1.66)<br>• Never: 0.42 (0.05–3.46) | 1996–1999; referent category = current smokers; structured health behavior assessment |
| Chade et al. 2010 | • 155 patients with carcinoma in situ of the bladder | C/F/N | • Former: 1.02 (0.63–1.66)<br>• Current: 0.86 (0.35–2.11) | 1990–2008; progression; chart review; patients treated with BCG |
| Hefler et al. 2010 | • 136 women with CIN I | Current/noncurrent | • 2.0 (1.1–3.7) | Progression; patients in phase II trial of progresterone |
| Ioffe et al. 2010 | • 130 Stage III-IV epithelial ovarian cancer patients | Current/notcurrent at surgery | • Current: 8 months<br>• Noncurrent: 19 months (p = 0.001) | 1996–2003; median time to progression; patients treated with cytoreductive surgery; chart review |

**Table 6.32*S* Continued**

| Study | Design/population | Smoking definition | Findings (all comparisons are vs. never unless otherwise specified) | Comments |
|---|---|---|---|---|
| Liao et al. 2010 | • 409 unresectable NSCLC patients | Current/noncurrent | • Recurrence: 0.80 (0.49–1.13)<br>• Distant metastasis: 0.89 (0.61–1.3) | 1999–2006; chart review; patients treated with RT |
| McCleary et al. 2010 | • 1045 participants with stage III colon cancer | C/F/N | • Former: 1.15 (0.89–1.48)<br>• Current: 0.90 (0.58–1.41) | CALGB 89803 trial treated with 5-FU/ leucovorin +/- irinotecan |
| Moreira et al. 2010 | • 1,276 prostate cancer patients | Current/noncurrent | • All patients: 1.19 (0.95–1.49)<br>• Obese patients: 1.37 (1.09–2.08) | 1998–2008; chart review; SEARCH study, treated with surgery |
| Murthy et al. 2010 | • 285 stage I NSCLC patients | Ever/never | • p = 0.007 | Recurrence |
| Sun et al. 2010 | • 250 stage IIIB-IV NSCLC patients | Ever/never | • Ever: 1.87 months<br>• Never: 3.27 months (p = 0.011 unadjusted, p = 0.92 adjusted) | 2007–2008; median time to progression; chart review; patients who failed chemotherapy and treated with pemetrexed |
| Hwang et al. 2011 | • 251 patients with NMIBC | Smoking history | • 1.63 (1.1–2.5) | 2000–2010; chart review; smoking not clearly defined; patients treated with surgery |
| Joshu et al. 2011 | • 1416 prostate cancer patients | C/F/N | • Never: 1.0 (referent)<br>• 5 years before surgery: 1.19 (0.55–2.57)<br>• 1 year after surgery: 2.31 (1.05–5.10) | 1993–2006; current reported as 5 years pre and 1 year post surgery; patients treated with surgery |
| Kenfield et al. 2011 | • 5,366 prostate cancer patients | C/F/N | • Former: 1.11 (0.96–1.29)<br>• Current: 1.61 (1.16–2.22) | Health Professionals Follow-Up Study; structured questionnaire every 2 years |
| Lammers et al. 2011 | • 718 NMIBC patients | Ever/never | • EORTC model: 1.47 (1.00–2.15)<br>• CUETO model: 1.57 (1.06–2.31) | 1998–2004; patients treated with surgery and enrolled on phase III trial of intravesicle chemotherapy |
| Maeda et al. 2011b | • 2,295 stage I-III NSCLC patients | Ever/never | • Stage I:<br>– 1.511 (1.033–2.210)<br>– Stage II:<br>– Ever: 40.2%<br>– Never: 55.8% (p = 0.049)<br>• Stage III:<br>– Ever: 68.6%<br>– Never: 83.5% (p = 0.004) | 1992–2006; ever smoking defined as >43 pack-years |
| Ngo et al. 2011 | • 630 prostate cancer patients | Pack-years | • Biochemical recurrence increase by 1% per pack year (p = 0.03) | 1989–2005; chart review |
| Schlumbrecht et al. 2011 | • 194 low grade serous adenocarcinoma of the ovary | Current/noncurrent | • 1.72 (1.00–2.96) | 1977–2009; progression |

**Table 6.32*S* Continued**

| Study | Design/population | Smoking definition | Findings (all comparisons are vs. never unless otherwise specified) | Comments |
|---|---|---|---|---|
| Sfakianos et al. 2011 | • 623 patients with high grade superficial, carcinoma in situ, or T1 invasive bladder cancer | C/F/N | • Former: 1.05 (0.84–1.32)<br>• Current: 1.04 (0.77–1.40) | 1994–2008; chart review; patients treated with BCG and surgery |
| Simsir et al. 2011 | • 140 patients with urothelial or TCC of the upper urinary tract | Ever/never | • Local Recurrence:<br>– Ever: 11.8 mon,ths<br>– Never: 19.5 months (p = 0.01)<br>• Metastasis:<br>– Ever: 19.6 months<br>– Never: 21.3 months (p = 0.24) | 2000–2007; recurrence (median time); chart review; patients treated with surgery |
| Hoff et al. 2012 | • 232 head/neck cancer patients treated with RT | Current/noncurrent | • 1.96 (1.09–3.52) | 1983–1991 |
| Hung et al. 2012 | • 756 stage I NSCLC patients | C/F/N | • Never: 1.0 (referent)<br>• 1–20 Pack-years: 1.039 (0.672–1.604)<br>• >20 Pack-years: 1.457 (1.069–1.986) | 1980–2010; patients treated with lobar resection |
| Segal et al. 2012 | • 278 high grade T1 bladder cancer patients | Ever/never | • 1.15 (0.75–1.76) | 1995–2000; progression; chart review |
| Varadarajan et al. 2012 | • 280 AML patients | Ever/never | • Ever: 43.01 months<br>• Never: 65.36 months (p = 0.02) | 1990–2008; median time to progression; chart review; patients treated with high dose cytarabine and idarubicin |

*Note*: **BCG** = Bacillus Colmette-Guerin; **CALGB** = cancer and leukemia group B; **C/F/N** = current/former/never; **CIN** = cervical intraepithelial neoplasia; **CIN I** = cervical dysplasia; **CML** = chronic myelogenous leukemia; **CUETO** = Spanish Urological Club for Oncological Treatment; **EORTC** = European Organisation for Research and Treatment of Cancer; **5-FU** = 5-fluorouracil; **GOG** = Gynecologic Oncology Grpup; **HLA** = human leukocyte antigen; **MIBC** = muscle-invasive bladder cancer; **NMIBC =** nonmuscle invasive bladder cancer; **NSCLS** = non-small-cell lung cancer; **pack-years** = the number of years of smoking multiplied by the number of packs of cigarettes smoked per day; **Recurrence** = local recurrence, distant recurrence, metastasis after diagnosis, progression, progression free survival, biochemical recurrence or progression, recurrence free survival; **RT** = radiotherapy.

**Table 6.33*S* Associations between smoking and cancer response**

| Study | Design/population | Smoking definition | Findings (all comparisons are vs. never unless otherwise specified) | Comments |
|---|---|---|---|---|
| Fountzilas et al. 1992 | • 115 Stage III-IV head/neck cancer patients | Ever/never | • 0.24 (p = 0.008) | 1984–1999; complete response to chemotherapy; patients treated with induction chemotherapy followed by surgery or RT |
| Browman et al. 1993 | • 115 Stage III-IV head/neck cancer patients | Current/noncurrent | • 0.61(p = 0.008) | Complete response; smoking during RT; patients treated with RT +/- chemotherapy |
| Scanlon et al. 1995 | • 835 breast cancer patients | Packs smoked | • 0: 1.0 (referent)<br>• <10,000: 1.06 (0.51–2.20)<br>• 10,001–20,000: 3.10 (1.54–6.25)<br>• >20,000: 3.73 (1.58–8.92) | 1982–1991; lung metastases after diagnosis. |
| Fountzilas et al. 1997 | • 154 Stage III-IV head/neck cancer patients | Ever/never | • 0.35 (p = 0.01) | 1984–1991; complete response; patients treated with induction chemotherapy followed by surgery or RT |
| Marshak et al. 1999 | • 207 T1-T2 laryngeal cancer patients | >30 Pack-years vs. ≤30 pack-years | • .90 (p = 0.043) | 1974–1994; local control; patients treated with RT |
| Ando et al. 2006 | • 1976 NSCLC patients | Ever/never | • 0.47 (0.34–0.65) | 2002; response. chart review; patients from 84 institutions treated with gefitinib |
| Lee et al. 2006 | • 575 stage IIIB-IV NSCLC patients | Ever/never | • Never: 2.48 (1.48-3.94)<br>• Ever: 1.0 (referent) | 2002-2005; response; chart review. patients treated with gefitinib |
| Duarte et al. 2008 | • 285 NSCLC patients | Ever/never | • <40 Pack-years: 1.0 (referent)<br>• ≥40: 0.096 (0.047–0.195) | 2000–2005; chart review; patients treated with chemotherapy +/- RT |
| Spigel et al. 2008 | • 229 stage IIIB-IV NSCLC patients | Ever/never | • 20 or less: 17.1%<br>• >20: 3.6% (no statistics) | 2004. response; analysis according to pack-years; patients treated on phase iii trial of erlotinib |
| Fortin et al. 2009 | • 1,871 head/neck cancer patients | C/F/N | • Never: 1.0 (referent)<br>• Former: 1.07<br>• Current: 0.89 (p <0.0000001) | 1989–2006; 5-year local control; chart review |
| Hayashibara et al. 2009 | • 626 NSCLC patients | Ever/never | • 0.71 (p = 0.006) | 2002–2007; response. chart review; patients treated with gefitinib |
| Khan et al. 2009 | • 80 women with vulvar intraepithelial neoplasia grade | Current/noncurrent | • 30.17 (2.07–439.56) | 1985–2005; persistent disease; smoking not clearly defined |

**Table 6.33*S* Continued**

| Study | Design/population | Smoking definition | Findings (all comparisons are vs. never unless otherwise specified) | Comments |
|---|---|---|---|---|
| Ang et al. 2010 | • 721 Stage III-IV head neck cancer patients | Pack-years | • Smoking decreased progression-free survival by 1% per pack year (p = 0.002) | Data from randomized cancer treatment trials of accelerated-fractionation RT with standard-fractionation RT, each combined with cisplatin therapy; smoking history used in recursive partition analysis |
| Liu et al. 2010b | • 698 patients with oral cavity cancer | Ever/never | • 1.18 (p = 0.36) | 1995–2005; 5-year local control; chart review; patients treated with surgery +/- adjuvant therapy |
| Matsumoto et al. 2010 | • 516 cervical low-grade squamous interceptihelial lesion patients | C/F/N | • Former: 0.73 (0.56–0.95)<br>• Current: 0.64 (0.44–0.93) | 1998–2004; Response; current include patients who quit in 12 months prior to diagnosis; Japan HPV and Cervical Cancer Study |
| Na et al. 2010 | • 162 female stage IIIB-IV NSCLC | Ever/never | • 1.10 (0.38–3.17) | 2002–2008; response; chart review; patients treated with gefitinib monotherapy |
| Algotar et al. 2011 | • 140 prostate cancer patients | Pack-years | • Never: 1.0 (referent)<br>• ≥49 Pack-years: 2.38 (p = 0.04) | Progression (PSA velocity) as fold-change; patients treated with watchful waiting |
| Sfakianos et al. 2011 | • 623 patients with high grade superficial, carcinoma in situ, or T1 invasive bladder cancer | C/F/N | • Former: 0.78 (0.49–1.24)<br>• Current: 0.90 (0.48–1.68) | 1994–2008; response; chart review; patients treated with BCG and surgery |

*Note:* **C/F/N** = current/former/never; **NSCLS** = non-small-cell lung cancer; **pack-years** = the number of years of smoking multiplied by the number of packs of cigarettes smoked per day; **PSA** = prostate-specific antigen; **Recurrence** = local recurrence, distant recurrence, metastasis after diagnosis, progression, progression free survival, biochemical recurrence or progression, recurrence free survival; **RT** = radiotherapy.

**Table 6.34*S* Associations between smoking and treatment-related toxicity in cancer patients**

| Study | Design/population | Smoking definition | Findings (all comparisons are vs. never unless otherwise specified) | Comments |
|---|---|---|---|---|
| Kearney et al. 1994 | • 331 pulmonary surgery patients | Ever/never | • Never: 9% (p<0.05)<br>• Ever: 20% | 1989–1991; postoperative complications. chart review |
| McCulloch et al. 1997 | • 114 head/neck cancer patients treated with surgery | Ever/never | • <50 Pack-years: 8.50<br>• >50 Pack-years: 24.3 (p <0.01) | 1985–1991; pulmonary complications; chart review |
| Bluman et al. 1998 | • 410 pulmonary surgery patients | C/F/N | • Never: 1.0<br>• Former: 1.9 (0.50–6.50)<br>• Current: 4.2 (1.20–14.80)<br>• Reduced: 6.7 (2.60–17.10) | 1990–1992; pulmonary complications. reduced smoking were patients who decreased tobacco use prior to surgery |
| van der Voet et al. 1998 | • 383 T1 laryngeal cancer patients treated with RT | Current/noncurrent | • Current: 1.0 (referent)<br>• Former: 0.50<br>• Quit after diagnosis: 0.39<br>• Never: 0.93 (p = 0.031) | 1965–1995; laryngeal complications; chart review; never smokers only with 12 patients |
| Fleshner et al. 1999 | • 286 superficial transitional cell cancer patients | Current/former | • 1.46 (0.98–2.14) | 1985–1995; adverse events; chart review |
| Harpole et al. 1999 | • 3516 patients treated with lobectomy or pneumonectomy | Current | • 1.27 (p=0.0049) | VA Surgical Quality Improvement Program database |
| Redaelli de Zinis et al. 1999 | • 246 head/neck cancer patients treated with laryngectomy | Ever/never | • 0.89 (p = 0.81) | 1988–1995; fistula formation; smoking not clearly defined |
| Bernard et al. 2001 | • 639 cancer patients treated with pneumonectomy | Not clearly defined | • "Factors not affecting morbidity or mortality included corticosteroid use, chronic renal failure, cirrhosis, nonpulmonary malignancy, smoking within 8 weeks of pneumonectomy, …" p. 1079 | 1985–1998; surgical complications. chart review |
| Myrdal et al. 2001 | • 616 lung or pleural cancer patients treated with surgery | Ever/never | • Ever: Univariate: 5.5 (1.3–22.8) | 1987–1999.;surgical complications. national registry data |
| Eifel et al. 2002 | • 3,489 stage I-II cervical cancer patients treated with RT | C/F/N | • Former: 1.40 (0.81–2.41)<br>• Current:<br>– <1 pack/day: 1.25 (0.88–1.79)<br>– ≥1 pack/day: 2.43 (1.95–3.04) | 1960–1994; pelvic complications; chart review |
| Griffin et al. 2002 | • 228 cancer patients with esophagectomy | Current/noncurrent | • 1.49 (p = 0.03) | 1990–2000; pulmonary complications |

**Table 6.34*S* Continued**

| Study | Design/population | Smoking definition | Findings (all comparisons are vs. never unless otherwise specified) | Comments |
|---|---|---|---|---|
| Sørensen et al. 2002 | • 425 patients with breast surgery | Current/noncurrent | • Infection:<br>– Nonsmoker: 1.0 (referent)<br>– 1–14 g/day: 2.95 (1.07–8.16)<br>– ≥15 g/day: 3.46 (1.52–7.85)<br>• Necrosis:<br>– Nonsmoker: 1.0 (referent)<br>– 1–14 g/day: 6.85 (1.96-23.90)<br>– ≥15 g/day: 9.22 (2.91–29.25)<br>• Epidermolysis:<br>– Nonsmoker: 1.0 (referent)<br>– 1–14 g/day: 3.98 (1.52–10.43)<br>– ≥15 g/day: 4.28 (1.81–10.13) | 1994–2006; surgical complications |
| Vaporciyan et al. 2002 | • 261 Stage I-III NSCLC patients | Quit duration | • 1+ month prior to surgery: 1.0 (referent)<br>• <1 month prior to surgery: 2.70 (1.18–6.17) | 1990–1999; pulmonary complications. chart review; comparisons based upon timing of cessation prior to pneumonectomy |
| Eckardt et al. 2003 | • 258 head/neck cancer patients with free flap reconstruction | Ever/never | • 1.94 (p = 0.043) | 1982–2000; overall complications; chart review; smoking not clearly defined |
| Garces et al. 2004 | • 1019 lung cancer patients | C/F/N | • Current: 28.7 (p<0.001)<br>• Former: 19.8<br>• Never: 20.0 | 1997–2002; lung cancer symptom score |
| Barrera et al. 2005 | • 300 primary or secondary lung cancer patients treated with thoracotomy | Pack-years | • Overall complications:<br>– 60 or less: 1.0<br>– >60: 2.54 (1.28–5.04)<br>• Pneumonia:<br>– 60 or less: 1.0<br>– >60: 3.10 (1.35–6.94) | 1999–2001; smoking cessation did not increase complication rate |
| Bullard et al. 2005 | • 160 rectal cancer patients treated with surgery | Ever/never | • 1.5 (0.76–2.98) | 1998–2002; wound complication; chart review; smoking not clearly defined |
| Goodwin et al. 2005 | • 515 breast cancer patients with breast reconstruction | Current/noncurrent | • 2.51 (p <0.001) | 2002–2003; total complications; current include quit <4 weeks |

**Table 6.34*S* Continued**

| Study | Design/population | Smoking definition | Findings (all comparisons are vs. never unless otherwise specified) | Comments |
|---|---|---|---|---|
| Kuri et al. 2005 | • 188 head/neck or esophageal cancer patients with free flap reconstruction | Current/ Noncurrent | • Current smokers: 1.0 (referent)<br>• Quit 8–21 days prior to operation: 0.31 (0.08–1.24)<br>• Quit 22–42 days prior to operation: 0.17 (0.04–0.75)<br>• Quit ≥43 days prior to operation: 0.17 (0.05–0.60)<br>• Nonsmokers: 0.11 (0.03–0.51) | 1996–2001; wound healing; chart review |
| Nickelsen et al. 2005 | • 5,181 colorectal cancer patients treated with surgery | C/F/N | • Former: 1.23 (1.03–1.47)<br>• Current: 1.35 (1.01–1.80) | 2001–2002; overall complications |
| Ando et al. 2006 | • 1976 NSCLC patients | Ever/Never | • 4.79 (1.69-13.54) | 2002; interstitial lung disease; chart review; patients from 84 institutions treated with gefitinib |
| Baser et al. 2006 | • 206 consecutive NSCLC patients | C/F/N | • Smoking cessation after diagnosis: 1.0 (referent)<br>• Continued smoking after diagnosis:<br>• 0-12 months: 6.99 (1.76–27.71) | 2001; decrease in performance status at 6 or 12 months. chart review |
| Gold et al. 2006 | • 2,198 stage I-IIIA breast cancer patients taking tamoxifen | C/F/N | • Former: 1.40 (1.10–1.78)<br>• Current: 2.12 (1.19–3.78) | 1995–2000; Vasomotor symptoms; Women's Healthy Eating and Living Study |
| Mason et al. 2006 | • 336 Stage I-IV NSCLC patients treated with pneumonectomy | Pack-years | • "Higher pack-years of smoking was identified as a preoperative risk factor for venous thromboemcolism" p. 713; "Risk factors for death included male sex, preoperative radiotherapy, lower forced expiratory volume in 1 second (percentage of normal value), higher pT, and increased pack-years of smoking (Table 2)" p. 7–13 p=0.02 | 1990-2001; chart review |
| Mehrara et al. 2006 | • 952 breast cancer patients with free flap reconstruction | Ever/Never | • No significant difference stated in text (p. 1103) | 1991–2002; overall complications; chart review |
| Pinsolle et al. 2006 | • 266 breast cancer patients with reconstruction | Current/ Noncurrent | • Skin necrosis: 2.86 (p = 0.02)<br>• Reconstruction failure: 4.82 (p = 0.015)<br>• Infection: 0.69 (not significant) | 1990–2002; reconstruction failure; chart review; current include patients quit <1 month |
| Song et al. 2006 | • 635 Stage I-IV NSCLC patients treated with surgery | C/FN | • Former: 2.76 (p <0.001)<br>• Current: 2.70 | 2001–2004; pulmonary complications; chart review |
| Clark et al. 2007 | • 185 head/neck cancer patients with free flap reconstruction | Current/ Noncurrent | • 2.34 (1.03–5.31) | 1999–2001; major complications; chart review |

**Table 6.34*S* Continued**

| Study | Design/population | Smoking definition | Findings (all comparisons are vs. never unless otherwise specified) | Comments |
|---|---|---|---|---|
| Kruschewski et al. 2007 | • 267 rectal cancer patients treated with surgery | Ever/never | • 6.42 (2.68–15.36) | 1995–2004; anastamotic leak |
| Lilla et al. 2007 | • 416 breast cancer patients treated with surgery + RT | C/F/N | • Former: 1.74 (0.99–3.04)<br>• Current: 1.45 (0.66–3.18) | 1998–2001; telangiectasia |
| Yildizeli et al. 2007 | • 218 NSCLC patients | Current/non-current | • Increased risk p=0.01 (p. 98) | 1981–2005; postoperative complications. chart review; patients treated with sleeve resection |
| Weinstein et al. 2007 | • 191 patients with lung surgery for primary or metastatic cancer | Not clearly defined | • "In univariate analysis, length of stay was increased by a history of heavy smoking (p=0.005), …" p. 199 | 1999–2002; chart review |
| Woerdeman et al. 2007 | • 309 breast cancer patients with mastectomy and immediate reconstruction | Ever/never | • 3.00 (1.61–5.57) | 2000–2004; implant failure |
| Zhan et al. 2007 | • 138 breast cancer patients taking tamoxifen | C/F/N | • Depression:<br>– Former: 3.1 (0.8–12.3)<br>– Current: 5.9 (1.4–24.3)<br>• Nausea:<br>– Former: 1.1 (0.2–5.9)<br>– Current: 5.9 (1.2–30.5)<br>• Migraines:<br>– Former: 1.1 (0.07–19.9)<br>– Current: 14.8 (1.5–148.1) | Tamoxifen side effect |
| Kirschbaum et al. 2008 | • 156 Stage I-II NSCLC patients treated with pneumonectomy | Current/noncurrent | • 30 day mortality: 1.6 (0.4–7.5)<br>• Complications: 2.4 (1.1–5.2) | 1995–2004; chart review |
| Marin et al. 2008 | • 89 stage III-IV head/neck cancer patients with reconstructive surgery | Current/noncurrent | • Self-reported:<br>– Never: 1.0 (referent)<br>– Former: 0.7 (0.2–1.9)<br>– Current: 1.3 (0.5–3.4)<br>• Cotinine validated (serum):<br>– 10 or less ng/ml: 1.0 referent)<br>– >10 ng/ml: 1.9 (1.1–3.3) | 1995–2008; wound complications |

**Table 6.34*S* Continued**

| Study | Design/population | Smoking definition | Findings (all comparisons are vs. never unless otherwise specified) | Comments |
|---|---|---|---|---|
| Martel et al. 2008 | • 220 rectal cancer patients treated with surgery | Current/noncurrent | • 6.37 (1.8–22.2) | 2000–2005; anastamotic leak; smoking not clearly defined, implied as current |
| McCarthy et al. 2008 | • 884 breast cancer patients with reconstruction | Current/noncurrent | • 2.2 (1.4–3.5) | 2003–2004; total complications; current include quit <4 weeks |
| Shimizu et al. 2008 | • 194 lung cancer patients treated with surgery | Ever/never | • 2.2 (p = 0.04) | 2003–2006. postoperative complications |
| Soensen et al. 2008 | • 208 gastrointestinal cancer patients treated with chemotherapy | Smoker/nonsmoker | • No significant difference stated in text (p. 1603) | 2001–2005; mucositis; smoking not clearly defined |
| Wright et al. 2008 | • 4,979 lung cancer patients with lobectomies | Ever/never | • 1.08 (p = 0.0007) | 2002–2006; length of hospital stay; Society of Thoracic Surgeons General Thoracic Surgery Database |
| Bagan et al. 2009 | • 159 NSCLC patients treated with surgery +/- chemotherapy | Ever/never | • "Overall operative morbidity was higher in the group of patients with a history of current smoking or recent smoking cessation" (p. 1734) | 1984–2005; chart review |
| Bianchi et al. 2009 | • 352 patients with free flap reconstructions | Smoking history | • 1.41 (p = 0.67) | 2000–2007; surgical complications; chart review |
| Cheung et al. 2009 | • 13,469 lung cancer patients treated with surgery | C/F/N | • Current: 1.0 (referent)<br>• Former: 0.84 (0.79–0.89)<br>• Never: 0.77 (0.69–0.86) | 1998–2002; postoperative death; chart review |
| Cooke et al. 2009 | • 1,133 cancer patients with esophagectomy | Current/noncurrent | • 1.46 (1.01–2.13) | 1996–2006; anastamotic leak; chart review |
| Hocevar-Boltezar et al. 2009 | • 75 T1 larynx cancer patients treated with RT | Current/noncurrent | • 1.59 (p = 0.02) | Poor voice quality; chart review |
| Joo et al. 2009 | • 111 laryngeal cancer patients treated with surgery | C/F/N | • Never: 0%<br>• Former: 30%<br>• Current: 37% (p = 0.02) | 1993–2008; pulmonary complications; chart review |
| Little et al. 2009 | • 205 patients with forehead flap reconstruction | Current/noncurrent | • 4.34 (1.26–14.93) | 1995–2008; flap necrosis; chart review |

**Table 6.34*S* Continued**

| Study | Design/population | Smoking definition | Findings (all comparisons are vs. never unless otherwise specified) | Comments |
|---|---|---|---|---|
| Marks et al. 2009 | • 2,818 HLA identical sibling or matched unrelated donor allogeneic transplants for CML | Ever (high dose, low dose)/never | • HLA-identical sibling donor group<br>– Low dose: 0.95 (0.77–1.88)<br>– High dose: 1.57 (1.14–2.14)<br>• Unrelated donor group<br>– Ever: 1.02 (0.79–1.33) | 1990–2004; treatment-related mortality |
| Mason et al. 2009 | • 7,990 lung cancer patients | C/F/N | • Hospital mortality, former:<br>– 14 days–1 month: 4.6 (1.2–18)<br>– 1 month–12 months: 2.6 (0.65–11)<br>– >12 months: 2.5 (0.82–7.6)<br>– Current: 3.5 (1.1–11)<br>• Pulmonary complications, former:<br>– 14 days–1 month: 1.6 (0.85–3.1)<br>– 1 month–12 months: 1.5 (0.81–2.8)<br>– >12 months: 1.3 (0.77–2.2)<br>– Current: 1.8 (1.05–3.1) | 1999–2007; Society of Thoracic Surgeons General Thoracic Surgery Database |
| Merkow et al. 2009 | • 23,098 patients with colorectal surgery | Current/noncurrent | • 1.32 (1.15–1.52) | 2006–2007; reoperation; current include smoking within past year; National Surgical Quality Improvement Program |
| Ogihara et al. 2009 | • 209 head/neck cancer patients treated with surgery | Ever/never | • 1.42 (p = 0.39) | 2002–2003; surgical site infection; chart review; smoking not clearly defined, implied as ever |
| Rabaglio et al. 2009 | • 4,895 breast cancer patients treated with surgery + estrogen receptor therapy | Ever/never | • 1.24 (1.00–1.52) | 1998–2003; fracture; breast international group 1–98 trial |
| Ulrich et al. 2009 | • 485 rectal cancer patients treated with surgery | Current/noncurrent | • Medical complication: 3.1 (1.4–6.4)<br>• Surgical complication: not significant | 2001–2006; complications |
| Wright et al. 2009 | • 2,315 patients treated with esophagectomy | Ever/never | • 1.27 (1.03–1.56) | 2002–2007; postoperative morbidity; smoking not clearly defined |
| Zevallos et al. 2009 | • 87 head neck cancer patients treated with RT | Current/noncurrent | • 1.3 (1.02–1.68) | Hospitalization during treatment; patients enrolled in structured tobacco cessation program |
| Baumann et al. 2010 | • 228 breast cancer patients with reconstructive surgery | Current/noncurrent | • 3.9 (1.3–2.4) | 2001–2006; fat necrosis; smoking not clearly defined |

**Table 6.34*S* Continued**

| Study | Design/population | Smoking definition | Findings (all comparisons are vs. never unless otherwise specified) | Comments |
|---|---|---|---|---|
| Begum et al. 2010 | • 374 ovarian cancer patients treated with surgery | C/F/N | • Former: 1.29 (0.69–2.40)<br>• Current (vs. former): 0.93 (0.49–1.77) | 1994–1999. postoperative complications |
| Berry et al. 2010 | • 705 breast cancer patients with mastectomy and reconstruction | Ever/never | • 2.17 (p = 0.10) | 2000–2006. surgical complications; chart review; never includes patients who quit >10 years prior to surgery |
| Bertelsen et al. 2010 | • 1,495 colorectal cancer patients treated with surgery | C/F/N | • Former: 1.46 (0.82–2.59)<br>• Current: 1.88 (1.02–3.46) | 2000–2004. anastamotic leak |
| Cowen et al. 2010 | • 141 breast cancer patients with mastectomy and immediate reconstruction followed by RT | Current/noncurrent | • 5.9 (2–17) | 1998–2006. reconstruction failure; smoking not clearly defined |
| Isobe et al. 2010 | • 865 lung cancer patients | Smoking index | • 0.2% cigarettes/day/year (p = 0.025) | 1999–2007. respiratory deterioration; chart review |
| Patel et al. 2010 | • 796 head/neck cancer patients with free flap reconstruction | Current/noncurrent | • 1.54 (1.02–2.32) | 1999–2007. surgical complications; chart review; smoking not clearly defined, implied as current |
| Wedlake et al. 2010 | • 193 patients treated with pelvic RT | C/F/N | • "Current smokers had the lowest presenting mean IBDQ-B score (63.7), suffered a fall during treatment (–12.0) and failed to recover at 1 year to within 3 points of presenting score (4.3-point difference between baseline and 1 year)." (p. 1167) | 2004–2006. bowel toxicity |
| Alsadius et al. 2011 | • 836 prostate cancer patients treated with external beam RT | Current/never | • Abdominal cramps: 9.0 (p = 0.004)<br>• Urgency: 2.65 (p <0.001)<br>• Diarrhea: 2.67 (p = 0.017)<br>• Incomplete emptying: 2.57 (p = 0.003)<br>• Sudden emptying: 4.6 (p = 0.003) | 1993–2006. rectal toxicity |
| Angarita et al. 2011 | • 199 breast cancer patients with mastectomy | Current/noncurrent | • 2.0 (p <0.0001) | 2005–2007. surgical site infections; chart review; current include patients who quit <6 months |
| Chen et al. 2011a | • 202 head/neck cancer patients treated with RT +/- surgery | Current/noncurrent | • Acute: 0.92 (p = 0.74)<br>• Late: 1.58 (p = 0.01) | 1998–2008. grade 3+ toxicity; chart review |
| Ehlers et al. 2011 | • 148 leukemia patients treated with stem cell transplant | C/F/N | • Former: 1.16<br>• Current: 1.80 (p = 0.009) | 1999–2005. hospitalization days; chart review; current include smoking within past year |

**Table 6.34*S* Continued**

| Study | Design/population | Smoking definition | Findings (all comparisons are vs. never unless otherwise specified) | Comments |
|---|---|---|---|---|
| Kasuya et al. 2011 | • 228 uterine or cervical cancer patients treated with surgery + RT | Smoker/nonsmoker | • 3.62 (1.32–10.0) | 1984–2004; radiation enterocolitis; chart review |
| Kelly et al. 2011 | • 2,322 patients with distal pancreatectomy | Current/noncurrent | • 1.29 (p = 0.013) | 2005–2008; morbidity and mortality combined; current include smoking within past year; national surgical quality improvement program |
| Kim et al. 2011 | • 215 colorectal cancer patients with surgery | C/F/N | • Former: 3.95 (0.52–30.1)<br>• Current: 2.28 (0.13–41.7)<br>• >40 Pack-years: 10.5 (1.11–99.6) | 2004–2009; anastamotic complications; chart review |
| Lee et al. 2011 | • 697 head/neck or thyroid cancer patients treated with surgery | Smoking history | • 2.34 (p <0.001 unadjusted, NS adjusted) | 2006–2009; surgical site infection; chart review; smoking not clearly defined |
| Millan et al. 2011 | • 773 colorectal cancer patients treated with surgery | Smoker/nonsmoker | • 1.55 (0.96–2.49) | 2006–2009; postoperative ileus; chart review; smoking not clearly defined |
| Richards et al. 2011 | • 423 stage I-III colorectal cancer patients treated with surgery | C/F/N | • Current: 1.32 (1.01–1.74) | 1997–2007; surgical complications. |
| Roxburgh et al. 2011 | • 302 colorectal cancer patients treated with surgery | Ever/never | • "Postoperative infective complications were associated with a smoking history, higher levels of deprivation, and increased burden of comorbidity measured by the NIA/NCI index only" (p. 1001) | 1997–2005 |
| Takamochi et al. 2011 | • 1,073 lung cancer patients treated with surgery | Pack year | • <70 years old:<br>– 40 or less Pack-years: 1.0 (referent)<br>– >40 Pack-years: 1.89 (1.35–2.65)<br>• ≥70 years old:<br>– 40 or less Pack-years: 1.0 (referent)<br>– >40 Pack-years: 2.18 (1.38–3.33) | 2006–2009; postoperative morbidity; chart review |
| Zingg et al. 2011 | • 858 patients treated with esophagectomy | Current/noncurrent | • 1.47 (1.08–2.01) | 1998–2008; overall pulmonary morbidity; smoking not clearly defined |

**Table 6.34*S* Continued**

| Study | Design/population | Smoking definition | Findings (all comparisons are vs. never unless otherwise specified) | Comments |
|---|---|---|---|---|
| Gajdos et al. 2012 | • 20,413 gastrointestinal, thoracic, and urologic cancer patients treated with major surgery | C/F/N | • Surgical site infection<br>– Gastrointestinal<br>o Former: 1.25 (1.09–1.44)<br>o Current: 1.20 (1.05–1.38)<br>– Thoracic<br>– Former: 0.69 (0.38–1.26)<br>– Current: 0.93 (0.54–1.60)<br>– Urologic<br>o Former: 1.18 (0.70–1.99)<br>o Current: 1.23 (0.78–1.93)<br>• Pulmonary complications<br>– Gastrointestinal<br>o Former: 1.60 (1.38–1.87)<br>o Current: 1.96 (1.68–2.29)<br>– Thoracic<br>o Former: 1.08 (0.81–1.42)<br>o Current: 1.62 (1.25–2.11)<br>– Urologic<br>o Former: 1.09 (0.63–1.86)<br>o Current: 1.57 (1.09–2.27)<br>• 30-day mortality<br>– Gastrointestinal<br>– Former: 1.50 (1.19–1.89)<br>– Current: 1.41 (1.13–1.82)<br>– Thoracic<br>o Former: 1.43 (0.88–2.34)<br>o Current: 1.30 (0.79–2.13)<br>– Urologic<br>o Former: 1.26 (0.68–2.34)<br>o Current: 1.19 1.16 (0.62–2.17) | VA Surgery Quality Improvement Program |
| Endoh et al. 2012 | • 296 NSCLC patients 75+ years old with pulmonary resection | Ever/never | • 3.11 (1.55–6.80) | 1998–2008; postoperative complications; chart review |
| le Nobel et al. 2012 | • 304 head/neck cancer patients with surgical reconstruction | Pack-years | • No significant difference stated in text (p. 1014) | 2003–2010; complications; chart review |

**Table 6.34*S* Continued**

| Study | Design/population | Smoking definition | Findings (all comparisons are vs. never unless otherwise specified) | Comments |
|---|---|---|---|---|
| Nakagawa et al. 2012 | • 3,488 unresectable, advanced, or recurrent NSCLC treated with erlotinib | Ever/never | • 2.99 (1.99–4.50) | 2007–2009; interstitial lung disease; smoking not clearly defined |
| Wuketich et al. 2012 | • 298 solid tumor cancer patients treated with chemotherapy | Current/noncurrent | • 2.82 ($p < 0.05$) | Mucositis |

*Note*: **C/F/N** = current/former/never; **HLA** = human leukocyte antigen; **g** = grams; **IBDQ-B** = Inflammatory Bowel Disease Questionnaire-Bowel subset; **NCI** = National Cancer Institute; **NIA** = National Institute on Aging; **NS** = not significant; **NSCLS** = non-small-cell lung cancer; **pack-years** = the number of years of smoking multiplied by the number of packs of cigarettes smoked per day; **RT** = radiotherapy.