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Red meat and cancer risk in a network of case–control studies focusing on cooking practices

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Background: Consumption of red meat has been related to increased risk of several cancers. Cooking methods could modify the magnitude of this association, as production of chemicals depends on the temperature and duration of cooking.

Methods: We analyzed data from a network of case–control studies conducted in Italy and Switzerland between 1991 and 2009. The studies included 1465 oral and pharyngeal, 198 nasopharyngeal, 851 laryngeal, 505 esophageal, 230 stomach, 1463 colon, 927 rectal, 326 pancreatic, 3034 breast, 454 endometrial, 1031 ovarian, 1294 prostate and 767 renal cancer cases. Controls included 11 656 patients admitted for acute, non-neoplastic conditions. Odds ratios (ORs) and confidence intervals (CIs) were estimated by multiple logistic regression models, adjusted for known confounding factors.

Results: Daily intake of red meat was significantly associated with the risk of cancer of the oral cavity and pharynx (OR for increase of 50 g/day = 1.38; 95% CI: 1.26–1.52), nasopharynx (OR = 1.29; 95% CI: 1.04–1.60), larynx (OR = 1.46; 95% CI: 1.30–1.64), esophagus (OR = 1.46; 95% CI: 1.23–1.72), colon (OR = 1.17; 95% CI: 1.08–1.26), rectum (OR = 1.22; 95% CI:1.11–1.33), pancreas (OR = 1.51; 95% CI: 1.25–1.82), breast (OR = 1.12; 95% CI: 1.04–1.19), endometrium (OR = 1.30; 95% CI: 1.10–1.55) and ovary (OR = 1.29; 95% CI: 1.16–1.43). Fried meat was associated with a higher risk of cancer of oral cavity and pharynx (OR = 2.80; 95% CI: 2.02–3.89) and esophagus (OR = 4.52; 95% CI: 2.50–8.18). Risk of prostate cancer increased for meat cooked by roasting/grilling (OR = 1.31; 95% CI: 1.12–1.54). No heterogeneity according to cooking methods emerged for other cancers. Nonetheless, significant associations with boiled/stewed meat also emerged for cancer of the nasopharynx (OR = 1.97; 95% CI: 1.30–3.00) and stomach (OR = 1.86; 95% CI: 1.20–2.87).

Conclusions: Our analysis confirmed red meat consumption as a risk factor for several cancer sites, with a limited impact of cooking methods. These findings, thus, call for a limitation of its consumption in populations of Western countries.

Key words: cancer, case–control study, cooking methods, red meat, risk

introduction

Consumption of red meat has been associated with increased risks of several tumors. The most convincing evidence is for colorectal cancer, but the results from both the cohort and case–control studies suggest a positive association also for cancers of the breast, pancreas, ovary, endometrium, esophagus and lung [1, 2]. Nonetheless, some inconsistencies do exist.

Several mechanisms have been suggested to explain the increased cancer risk associated with elevated red meat consumption, including high intake of proteins and fats and intake of carcinogens due to cooking at high temperatures [3]. In particular, meat cooking practices may vary across populations, and they may partly explain the heterogeneity among studies. Protein-rich foods generate heterocyclic amines (HCAs), polycyclic aromatic hydrocarbons (PAHs) and N-nitroso compounds (NOCs) when cooked at high temperatures (e.g. grilling) or when heated for a prolonged time (e.g. stewing) [4]. Temperature is the most important factor in the formation of HCA, a group of chemicals produced by a reaction of amino acids and creatinine at elevated temperatures.

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PAHs also derive from incomplete burning of organic substances, mainly from meat grilling or broiling. Red meat is also rich in iron and nitrate/nitrite, which are involved in the endogenous formation of NOCs [3, 5].

To add information on this topic, we investigated the association between red meat intake and the risk of various cancers using data from a network of case–control studies conducted in Italy and Switzerland, focusing on the major cooking practices.

materials and methods

Between 1991 and 2009, we conducted an integrated series of case–control studies on various neoplasms in different areas of northern (the greater Milan area; the provinces of Pordenone, Padua, Udine, and Forlì; the urban area of Genoa), central (the provinces of Rome and Latina) and southern (the urban area of Naples and Catania) Italy, and in the Swiss Canton of Vaud. The studies included 1468 cases of cancer of the oral cavity and pharynx [6, 7], 198 of the nasopharynx [8], 852 of the larynx [9], 505 of the esophagus [10, 11], 230 of the stomach [12], 1463 of the colon [13, 14], 927 of the rectum [13, 14], 326 of the pancreas [15], 3034 of the breast [16, 17], 454 of the endometrium [18], 1031 of the ovary [19], 1294 of the prostate [20], 767 of the kidney [21] and 11 656 frequency-matched controls, which were included in more than one study. Three cases of oropharyngeal cancer and one case of laryngeal cancer were excluded because of incomplete data on red meat consumption (Table 1).

All studies included incident cancer cases, identified in the major teaching and general hospitals of the study areas. Controls were subjects admitted to the same network of hospitals as cases for a wide spectrum of acute, non-neoplastic conditions unrelated to tobacco and alcohol consumption, to known risk factors for the corresponding cancer site or to conditions associated with long-term diet modification. Overall, 8.0% of controls were admitted for traumatic conditions, 22.5% for non-traumatic orthopedic conditions, 32.8% for acute surgical conditions and 36.7% for miscellaneous other illnesses. In each study, refusal rates for both cases and controls were similar, ranging between 2% and 5% in Italy and between 11% and 15% in Switzerland. Study protocols were approved by the Board of Ethics of the hospitals involved. All participants signed an informed consent.

Table 1. Distribution of cases and corresponding controls by sex and age according to cancer sites

Cancer site (references)	Cases		Controls	
	Men/women	Median age (years)	Men/women	Median age (years)
Oral cavity and pharynx [6, 7]	1187/278	58	2553/1208	58
Nasopharynx [8]	157/41	52	471/123	52
Larynx [9]	769/82	62	1564/406	61
Esophagus [10, 11]	438/67	60	919/340	60
Stomach [12]	143/87	63	286/261	63
Colon [13, 14]	835/628	62	2586/2357	58
Rectum [13, 14]	566/361	63	2586/2357	58
Pancreas [15]	174/152	63	348/304	63
Breast [16, 17]	-/3034	55	-/3392	56
Endometrium [18]	-/454	60	-/908	61
Ovary [19]	-/1031	56	-/2411	57
Prostate [20]	1294/-	66	1451/-	63
Kidney [21]	494/273	62	988/546	62

Italy and Switzerland, 1991–2009.

Trained personnel administered a structured questionnaire to cases and controls during hospitalization. Interviewers were not blinded to case status. The questionnaire included information on socio-demographic characteristics, anthropometric measures, lifestyle habits (e.g. tobacco smoking, alcohol drinking), personal medical history, family history of cancer, and, for women, menstrual and reproductive factors, use of oral contraceptives (OCs) and hormone replacement therapy (HRT). Subjects' usual diet in the 2 years before diagnosis (or hospital admission, for controls) was investigated using a food frequency questionnaire (FFQ), which included specific food items on weekly consumption of red meat according to different cooking methods (i.e. boiling/stewing, roasting/grilling, or frying/pan frying - supplementary Table S1, available at *Annals of Oncology* online). Serving size was defined as an average serving in the Italian diet (e.g. 150 g for grilled steak; 120 g for boiled meat). Total red meat was calculated as the sum of food items for beef, veal, pork, horsemeat, and half of the first course including meat sauce (e.g. lasagne, pasta/rice with bologna sauce). The FFQ was successfully tested for validity [22] and reproducibility [23]. Total red meat intake was expressed in grams per day (g/day), and it did not include processed meat.

Odds ratios (ORs) for an increase of 50 g/day of red meat intake, and the corresponding 95% confidence intervals (CIs), were estimated by unconditional multiple logistic regression models [24]. The original control group was used for comparison in each cancer site (Table 1). Red meat intake was further categorized in approximate tertiles of consumption among all controls. The models included terms for study centre, age, sex (when appropriate), education, year of interview, body mass index, tobacco smoking, alcohol drinking, fruit and vegetable consumption [1]. ORs for cancer of the breast, endometrium and ovary were further adjusted for menopausal status, parity, and use of OCs or HRT. The test for trend was based on the likelihood-ratio test between the models with and without linear terms for each variable of interest [24].

results

Table 2 shows the median daily intake of red meat for cancer cases and controls in the 13 included studies. Patients with cancer of the oral cavity and pharynx, nasopharynx, larynx, esophagus, stomach, rectum, pancreas, breast, endometrium and ovary reported higher intake of red meat than the corresponding controls. After adjustment for relevant risk factors, a direct association between red meat intake and cancer risk emerged for oral cavity and pharynx (OR for increase of 50 g/day = 1.38; 95% CI: 1.26–1.52), nasopharynx (OR = 1.29; 95% CI: 1.04–1.60), larynx (OR = 1.46; 95% CI: 1.30–1.64), esophagus (OR = 1.46; 95% CI: 1.23–1.72), colon (OR = 1.17; 95% CI: 1.08–1.26), rectum (OR = 1.22; 95% CI: 1.11–1.33), pancreas (OR = 1.51; 95% CI: 1.25–1.82), breast (OR = 1.12; 95% CI: 1.04–1.19), endometrium (OR = 1.30; 95% CI: 1.10–1.55) and ovary (OR = 1.29; 95% CI: 1.16–1.43). These associations were confirmed when red meat intake was categorized in approximate tertiles of intake for all cancer sites but nasopharynx. Risk estimates for cancer of the stomach and prostate were above unity, but did not reach statistical significance. No associations emerged for renal cancer.

ORs across strata of sex, age, tobacco smoking, alcohol drinking or fruit and vegetable consumption were not heterogeneous. Only for laryngeal cancer, the association was stronger among women than among men (supplementary Table S2, available at *Annals of Oncology* online). For breast cancer, the association was consistent in premenopausal

Table 2. Median daily intake of red meat (g), odds ratio (OR) and corresponding 95% CI[a] for selected cancer sites

Cancer site	Red meat, median intake (g/day)			Red meat intake (g/day)					χ^2 trend	Increase of 50 g/day OR (95% CI)
				<60[b]	60–89		≥90			
	Ca	Co	M-W	Ca:Co	Ca:Co	OR (95% CI)	Ca:Co	OR (95% CI)		
Oral cavity and pharynx	90.0	78.6	$P < 0.01$	294:1104	434:1265	1.25 (1.02–1.52)	737:1392	1.83 (1.51–2.23)	$P < 0.01$	1.38 (1.26–1.52)
Nasopharynx[c]	87.9	76.8	$P < 0.01$	48:175	53:188	1.03 (0.64–1.66)	97:231	1.48 (0.95–2.31)	$P = 0.06$	1.29 (1.04–1.60)
Larynx	95.7	77.9	$P < 0.01$	154:651	229:580	1.68 (1.28–2.20)	468:739	2.34 (1.82–3.00)	$P < 0.01$	1.46 (1.30–1.64)
Esophagus	92.9	81.4	$P < 0.01$	93:309	144:431	1.25 (0.87–1.79)	268:519	2.01 (1.43–2.84)	$P < 0.01$	1.46 (1.23–1.72)
Stomach	72.0	61.1	$P < 0.01$	95:264	70:165	1.15 (0.79–1.67)	65:118	1.38 (0.92–2.07)	$P = 0.12$	1.22 (0.98–1.53)
Colon	77.5	77.1	$P = 0.13$	446:1648	443:1426	1.19 (1.02–1.38)	554:1869	1.22 (1.05–1.41)	$P = 0.02$	1.17 (1.08–1.26)
Rectum	80.7	77.1	$P < 0.01$	268:1648	279:1426	1.25 (1.04–1.51)	380:1869	1.35 (1.12–1.62)	$P < 0.01$	1.22 (1.11–1.33)
Pancreas[c]	79.6	67.1	$P < 0.01$	96:274	96:197	1.42 (0.98–2.07)	134:181	2.18 (1.51–3.16)	$P < 0.01$	1.51 (1.25–1.82)
Breast[d]	76.1	72.9	$P < 0.01$	1019:1178	903:1124	0.93 (0.82–1.05)	1112:1090	1.18 (1.04–1.33)	$P < 0.01$	1.12 (1.04–1.19)
Endometrium[d]	73.6	68.8	$P < 0.01$	148:358	143:304	1.05 (0.79–1.41)	163:246	1.71 (1.26–2.33)	$P < 0.01$	1.30 (1.10–1.55)
Ovary[d]	72.5	65.4	$P < 0.01$	364:1047	346:723	1.34 (1.11–1.61)	321:641	1.49 (1.23–1.80)	$P < 0.01$	1.29 (1.16–1.43)
Prostate	73.6	73.9	$P = 0.98$	456:524	385:414	1.17 (0.96–1.42)	453:513	1.15 (0.96–1.39)	$P = 0.14$	1.07 (0.97–1.18)
Kidney	71.4	72.9	$P = 0.34$	285:545	245:463	1.03 (0.83–1.28)	237:526	0.89 (0.72–1.12)	$P = 0.34$	0.98 (0.87–1.10)

[a]Adjusted for study centre, age (quinquennia), sex (when appropriate), education (< 7, 7–11, ≥12 years), body mass index (<25, 25–<30, ≥30 kg m^{-2}), tobacco smoking (never, former, current: <15, ≥15 cigarettes/day), alcohol drinking (never, former, current: <3, 3–4, 5–7, ≥8 drinks/day), vegetable consumption (<1.5, 1.5–<3, ≥3 servings/day) and fruit consumption (<3, 3–<4, ≥4 servings/day).
[b]Reference category.
[c]Additionally adjusted for year of interview.
[d]Additionally adjusted for menopausal status (pre-/perimenopause; postmenopause), parity (0–1, 2, ≥3) and OC/HRT use (never, ever).
Ca, cases; Co, controls; M–W, Mann–Whitney test; OR, odds ratio; CI, confidence interval; OC, oral contraceptives; HRT, hormone replacement therapy.

(OR = 1.14; 95% CI: 1.02–1.28) and postmenopausal women (OR = 1.10; 95% CI: 1.01–1.19). Conversely, the association between red meat and the risk of endometrial (OR = 1.45; 95% CI: 1.19–1.77) and ovarian cancers (OR = 1.47; 95% CI: 1.28–1.68) was found only among postmenopausal women (supplementary Table S2, available at *Annals of Oncology* online).

The relationship between red meat consumption and cancer risk was additionally investigated according to cooking practices (Figure 1). A modifying effect of cooking methods emerged for cancer of the oral cavity and pharynx (P for heterogeneity < *0.01*), esophagus ($P < 0.01$) and prostate ($P < 0.01$). ORs of fried red meat were higher than those of other cooking practices for cancer of the oral cavity and pharynx (OR = 2.08; 95% CI: 2.02–3.89) and esophagus (OR = 4.52; 95% CI: 2.50–8.18). Conversely, the risk of prostate cancer was associated with red meat cooked by roasting/grilling (OR = 1.31; 95% CI: 1.12–1.54), but not with boiled/stewed and fried meat. For other cancer sites, cooking methods did not substantially modify the association between cancer risk and meat consumption (P for heterogeneity ≥*0.05*), even if fried meat showed ORs higher than other cooking methods for cancers of the rectum, endometrium and ovary (Figure 1). However, meat frying was less common in Italy than other cooking practices, as proved by wider CIs, and their risk estimates may have been affected by casual variation. Although not significantly associated with overall red meat consumption, stomach cancer showed a significant association with boiled/stewed meat (OR = 1.86; 95% CI: 1.20–2.87).

discussion

The results of the present study confirm the well-known relationship between red meat consumption and colorectal cancer [2]. They also support the association with cancer of the upper aero-digestive tract, breast, pancreas, endometrium and ovary. Cooking practices had a limited impact on these relationships.

The substantial amount of epidemiological data supports the evidence that red meat consumption contributes to colorectal etiology [2]. Production of carcinogens during meat cooking at high temperatures is a plausible mechanism to explain this association [3], but the results from epidemiological studies are inconsistent. Alternative mechanisms include endogenous production of NOCs and elevated intake of protein, fat and heme iron [3], which may couple with the lack of heterogeneity across the cooking methods reported in the present study.

In this analysis, red meat was associated with the risk of the upper aero-digestive tract cancers, such as oral cavity and pharynx, larynx and esophagus. Red meat has been recognized as a potential risk factor for esophageal cancer [2], but not for other upper aero-digestive cancers. Nonetheless, an early study in Brazil [25] reported elevated risk of oral cancer among people eating grilled meat more than four times per week compared with less than one time per month. Likewise, an increased consumption of broiled or boiled meat was associated with a twofold increase in the risk of cancers of the upper aero-digestive tract in a case–control study in Uruguay [26]. This study also reported an association between the risk of upper aero-digestive tract cancer and total HCAs, as estimated from a

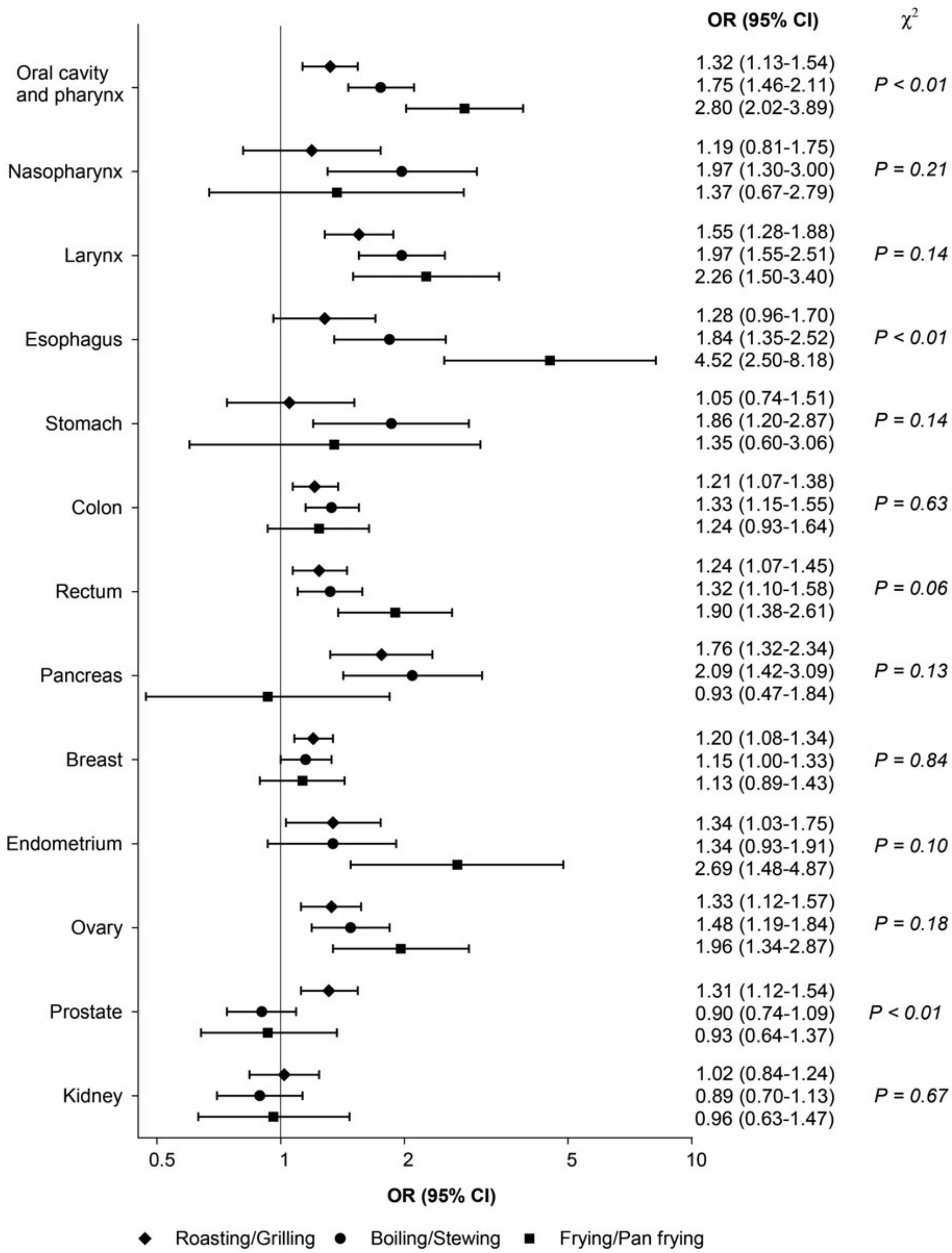

Figure 1. ORs and 95% CI for a daily increase of 50 g of red meat, according to cooking practices. Risk estimates were adjusted for covariates reported in Table 2. Heterogeneity of ORs across different cooking methods was evaluated through X^2 test. OR, odds ratio; CI, confidence interval.

FFQ [26]. A recent study in Uruguay reported an elevated risk of esophageal cancer for elevated red meat consumption, irrespective of cooking methods [27].

Current evidence suggests a positive association between red meat intake and cancers of the breast, ovary and endometrium [1, 2]. In the Nashville Breast Health Study, a 50% increase in breast cancer risk was observed among women with elevated consumption of red meat [28]. This excess of risk was not significantly different according to cooking methods, and the results were similar for either premenopausal or postmenopausal women. In a case–control study conducted in Shanghai [29], red meat was associated to increased risk of endometrial cancer; cooking methods had a minimal influence on the observed risk. Cancers of the breast, endometrium and ovary are hormone-related and elevated protein intake has been associated with these cancers [2]. The absence of any modifying effect of cooking practices in the association between cancer risk and red meat consumption may reflect an increase in endogenous estrogen levels due to elevated meat consumption [30].

Pancreatic cancer has been consistently associated with elevated red meat consumption [2, 15, 31], and the relation was more evident for meat cooked by stewing, broiling or roasting rather than by frying [15, 32]. A number of studies [32, 33] reported elevated risk of pancreatic cancer for high intake of dietary HCAs and PHAs, and these results were consistent with the findings from animal models, showing carcinogenic effects for several HCAs and PAHs [34].

In the present study, the risk of prostate cancer was associated to roasted/grilled red meat, but not to meat cooked by boiling/stewing or frying. This finding couples with the results from a recent case–control study conducted in the United States [35], which reported a non-significant increased risk of prostate cancer for consumption of beef, pork and lamb (OR = 1.25; 95% CI: 0.74–2.11). Nonetheless, significant associations emerged for consumption of grilled or barbequed meat, and the risks increased with levels of doneness [35].

The absence of information on the degree of meat doneness is a potential limitation of this study. The formation of HCAs and PAHs increases with temperature and duration of cooking, so that information on the degree of doneness would be of interest. Likewise, the lack of a direct estimation of the amount of carcinogens assumed through cooked meat consumption is a weakness of this analysis. Several factors may increase or decrease the formation of HCAs and PAHs, including meat type and use of seasonings.

Other potential limitations of these series of case–control studies comprise information and selection biases. Information bias, however, was minimized through the direct interview of cases and controls by the same trained interviewers, under similar conditions in a hospital setting. Careful attention was also paid in excluding from the control group subjects admitted for any condition that might have induced a modification of the usual diet. In addition, the almost complete case ascertainment in the catchment areas, the nearly complete participation of identified cases and controls, and the use of a validated and reproducible questionnaire contributed to strengthen our findings [22, 23].

In conclusion, the results of the present analysis suggested that red meat is a risk factor for cancer, with a limited impact of the cooking methods, thus claiming for a limitation of this food in the diet of Western country populations.

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disclosure

The authors have declared no conflicts of interest.

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Suicide and suicide attempt after a cancer diagnosis among young individuals

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Background: Data are scarce on the potential change in suicidal behavior among adolescents and young adults after receiving a cancer diagnosis.

Patients and methods: We conducted a population-based cohort study including 7 860 629 Swedes at the age of ≥15 during 1987–2009. Among the cohort participants, 12 669 received a first diagnosis of primary cancer between the age of 15 and 30. We measured the relative risks (RRs) of suicidal behavior (defined as completed suicides or suicide attempts) after cancer diagnosis. We also carried out a case-crossover study nested within the cohort to adjust for unmeasured confounders.

Results: Twenty-two completed suicides (versus 14 expected) and 136 suicide attempts (versus 80 expected) were identified among the cancer patients. The RR of suicidal behavior was 1.6 [95% confidence interval (CI), 1.4–1.9] after a cancer diagnosis, compared with cancer-free individuals. Risk increase was greatest immediately after diagnosis; the RR was 2.5 (95% CI 1.7–3.5) during the first year after diagnosis and was 1.5 (95% CI 1.2–1.8) thereafter. This pattern was similar for completed suicide and suicide attempts. The elevated risks were evident for majority of the main cancer types, except for cancer in thyroid, testis and melanoma. The case-crossover analysis of suicidal behavior during the first year after cancer diagnosis revealed similar results.

Conclusions: Adolescents and young adults receiving a cancer diagnosis are at substantially increased risk of suicidal behavior, particularly during the first year after diagnosis. Although the absolute excess risk is modest, these findings emphasize the need to support and carefully monitor this vulnerable population.

Key words: cancer diagnosis, adolescents, psychological stress, suicidal behavior, young adults

introduction

Receiving a cancer diagnosis is a stressful event [1, 2]. The distress may not only impair the quality of life [3], accelerate disease progression [4], but also cause non-cancer mortality including suicide [5]. Suicide risk among cancer patients is estimated to be twice the general US population [6], with the immediate time period after cancer diagnosis appears to be most critical [7]. However, the existing literature has mostly focused on adult cancer patients [7–9], and to our knowledge, few studies have specifically investigated adolescents and young adults [10].

Suicide is the second most common cause of death in young people worldwide [11]. In Sweden, the rate of suicidal behavior among young adults of age 19–23 increased continuously between 1995 and 2005, contrasting the declining rate in all other age groups [12]. Because adolescents and young adults are still developing their coping strategies for stress [13], they may be more affected than adults when facing major adversity such as a cancer diagnosis.

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