Cancer is a major risk factors for thrombotic pulmonary embolism (PE), tumor PE and tumor invasion into large veins according to tumor type and tumor site remains unclear.

**Methods and Results**
A total of 65,181 cancer patients were identified from 98,736 postmortem examinations. Thrombotic PE occurred in 2.32% of all cancer patients and comprised 88.6% of the total number of all PE events. The incidence of thrombotic PE was high in those with adenocarcinoma, leukemia and large cell carcinoma, and was low in those with hepatic cell carcinoma. The incidence of PE was high when tumor was present in hematogenous tissue, lungs, ovaries, pancreas and the biliary system, and was low when tumor was present in the liver. The incidence of tumor PE was high with large cell carcinoma, hepatic cell carcinoma and adenocarcinoma, and was also high when tumor was present in the lungs, ovaries, kidneys and liver. There was a significant correlation between the incidence of tumor PE and the incidence of tumor invasion into large veins.

**Conclusion**
The incidence of thrombotic PE, tumor PE and tumor invasion into large veins varies significantly according to tumor histopathology and tumor site. (Circ J 2006; 70: 744–749)

**Key Words:** Adenocarcinoma; Autopsy; Hepatic cell carcinoma; Leukemia; Pancreas

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**Background**
The specific incidence of thrombotic pulmonary embolism (PE), tumor PE and tumor invasion into large veins according to tumor type and tumor site remains unclear.

**Methods**
A total of 65,181 cancer patients (66.0%) were identified from 98,736 postmortem examinations. The incidence of thrombotic PE occurred in 2.32% of all cancer patients and comprised 88.6% of the total number of all PE events. The incidence of thrombotic PE was high in those with adenocarcinoma, leukemia and large cell carcinoma, and was low in those with hepatic cell carcinoma. The incidence of PE was high when tumor was present in hematogenous tissue, lungs, ovaries, pancreas and the biliary system, and was low when tumor was present in the liver. The incidence of tumor PE was high with large cell carcinoma, hepatic cell carcinoma and adenocarcinoma, and was also high when tumor was present in the lungs, ovaries, kidneys and liver. There was a significant correlation between the incidence of tumor PE and the incidence of tumor invasion into large veins.

**Conclusion**
The incidence of thrombotic PE, tumor PE and tumor invasion into large veins varies significantly according to tumor histopathology and tumor site. (Circ J 2006; 70: 744–749)

**Key Words:** Adenocarcinoma; Autopsy; Hepatic cell carcinoma; Leukemia; Pancreas

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Cancer is a major risk factors for thrombotic pulmonary embolism (PE),1–4 and thrombotic PE associated with cancer is known as Trousseau’s syndrome. Cancer induces not only thrombotic PE but also tumor PE and tumor invasion into large veins. However, there is lack of epidemiological data from the general population to compare the incidence of thrombotic PE, tumor PE and tumor invasion to large veins according to the histopathology and the site of the cancer. Clinicians have given more attention to the prevention of venous thromboembolism (VTE) with chemotherapeutic and surgical treatment of cancer patients, but it is important to evaluate the risk of the development of VTE according to the histopathology and primary site of the cancer.

The goal of this study was to investigate variations in the incidence of thrombotic PE, tumor PE and tumor invasion into large veins according to tumor histopathology and tumor site.

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Fig 1. Age distribution of all cases with pulmonary embolism.
Cancer and Pulmonary Embolism

### Table 1 Incidence of Pulmonary Embolism (PE) for Each Tumor Type

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>Total cases</th>
<th>Total PE</th>
<th>Critical PE</th>
<th>Thrombotic PE</th>
<th>Tumor PE</th>
<th>Tumor invasion into a large vein</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malignant lymphoma</td>
<td>3,463</td>
<td>80</td>
<td>(2.31; 2.80–2.82)</td>
<td>(0.64; 0.37–0.90)</td>
<td>(2.11; 1.62–2.59)</td>
<td>(0.06; 0.00–0.14)</td>
</tr>
<tr>
<td>Myeloma</td>
<td>1,030</td>
<td>33</td>
<td>(3.20; 2.11–3.40)</td>
<td>(0.97; 0.37–1.57)</td>
<td>(3.01; 1.95–4.07)</td>
<td>(0.19; 0.00–0.46)</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>23,535</td>
<td>858</td>
<td>(3.65; 3.40–3.89)</td>
<td>(1.07; 0.94–1.21)</td>
<td>(3.35; 3.11–3.58)</td>
<td>(0.23; 0.15–0.26)</td>
</tr>
<tr>
<td>Leukemia</td>
<td>3,782</td>
<td>178</td>
<td>(4.71; 4.02–5.40)</td>
<td>(1.56; 1.16–1.96)</td>
<td>(3.81; 3.19–4.43)</td>
<td>(0.05; 0.00–0.13)</td>
</tr>
<tr>
<td>Transitional cell carcinoma</td>
<td>1,294</td>
<td>27</td>
<td>(2.09; 1.30–2.87)</td>
<td>(1.39; 0.75–2.03)</td>
<td>(1.93; 1.17–2.69)</td>
<td>(0.16; 0.00–0.37)</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>7,055</td>
<td>155</td>
<td>(2.20; 1.85–2.54)</td>
<td>(0.48; 0.32–0.64)</td>
<td>(2.04; 1.71–2.37)</td>
<td>(0.07; 0.01–0.13)</td>
</tr>
<tr>
<td>Hepatic cell carcinoma</td>
<td>7,971</td>
<td>81</td>
<td>(1.02; 0.79–1.24)</td>
<td>(0.23; 0.12–0.33)</td>
<td>(0.65; 0.48–0.83)</td>
<td>(0.33; 0.20–0.45)</td>
</tr>
<tr>
<td>Small cell carcinoma</td>
<td>1,846</td>
<td>47</td>
<td>(2.65; 1.91–3.40)</td>
<td>(0.81; 0.40–1.22)</td>
<td>(2.49; 1.77–3.21)</td>
<td>(0.05; 0.00–0.16)</td>
</tr>
<tr>
<td>Micinous carcinoma</td>
<td>1,412</td>
<td>73</td>
<td>(3.33; 2.38–4.28)</td>
<td>(1.27; 0.69–1.86)</td>
<td>(3.05; 2.14–3.96)</td>
<td>(0.21; 0.01–0.45)</td>
</tr>
<tr>
<td>Large cell carcinoma</td>
<td>714</td>
<td>33</td>
<td>(4.62; 3.04–6.20)</td>
<td>(0.98; 0.25–1.71)</td>
<td>(4.06; 2.58–5.54)</td>
<td>(0.56; 0.01–1.11)</td>
</tr>
<tr>
<td>p value</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data are number (%; 95% confidence interval) of patients.

### Table 2 Incidence of Pulmonary Embolism (PE) According to Tumor Site

<table>
<thead>
<tr>
<th>Tumor site</th>
<th>Total cases</th>
<th>Total PE</th>
<th>Critical PE</th>
<th>Thrombotic PE</th>
<th>Tumor PE</th>
<th>Tumor invasion into a large vein</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>9,355</td>
<td>106</td>
<td>(1.13; 0.92–1.35)</td>
<td>(0.24; 0.14–0.33)</td>
<td>(0.77; 0.59–0.95)</td>
<td>(0.34; 0.22–0.46)</td>
</tr>
<tr>
<td>Breast</td>
<td>1,480</td>
<td>43</td>
<td>(2.91; 2.04–3.77)</td>
<td>(1.15; 0.60–1.69)</td>
<td>(2.57; 1.75–3.38)</td>
<td>(0.14; 0.00–0.32)</td>
</tr>
<tr>
<td>Thyroid</td>
<td>1,781</td>
<td>54</td>
<td>(3.03; 2.22–3.84)</td>
<td>(1.40; 0.85–1.95)</td>
<td>(2.81; 2.03–3.59)</td>
<td>(0.11; 0.00–0.27)</td>
</tr>
<tr>
<td>Hematogenous tissue</td>
<td>4,944</td>
<td>223</td>
<td>(4.51; 3.92–5.10)</td>
<td>(1.46; 1.12–1.79)</td>
<td>(3.72; 3.18–4.26)</td>
<td>(0.06; 0.00–0.13)</td>
</tr>
<tr>
<td>Brain</td>
<td>1,199</td>
<td>20</td>
<td>(1.67; 0.94–2.40)</td>
<td>(0.58; 0.15–1.02)</td>
<td>(1.75; 1.00–2.50)</td>
<td>(0.00; –)</td>
</tr>
<tr>
<td>Lung</td>
<td>10,180</td>
<td>352</td>
<td>(3.46; 2.10–3.82)</td>
<td>(0.83; 0.55–1.00)</td>
<td>(3.24; 2.89–3.59)</td>
<td>(0.16; 0.08–0.23)</td>
</tr>
<tr>
<td>Uterus</td>
<td>1,318</td>
<td>42</td>
<td>(3.19; 2.22–4.15)</td>
<td>(1.29; 0.68–1.90)</td>
<td>(3.03; 2.09–3.98)</td>
<td>(0.08; 0.00–0.22)</td>
</tr>
<tr>
<td>Digestive system</td>
<td>16,440</td>
<td>447</td>
<td>(2.72; 2.47–2.97)</td>
<td>(0.88; 0.73–1.02)</td>
<td>(2.45; 2.21–2.68)</td>
<td>(0.20; 0.13–0.27)</td>
</tr>
<tr>
<td>Ovary</td>
<td>835</td>
<td>48</td>
<td>(5.75; 4.14–7.37)</td>
<td>(1.80; 0.89–2.71)</td>
<td>(5.39; 3.81–6.96)</td>
<td>(0.48; 0.01–0.93)</td>
</tr>
<tr>
<td>Kidney</td>
<td>1,488</td>
<td>32</td>
<td>(2.15; 1.41–2.90)</td>
<td>(1.01; 0.50–1.52)</td>
<td>(1.81; 1.13–2.50)</td>
<td>(0.47; 0.12–0.82)</td>
</tr>
<tr>
<td>Prostate</td>
<td>2,290</td>
<td>63</td>
<td>(2.75; 2.07–3.43)</td>
<td>(1.22; 0.77–1.68)</td>
<td>(2.58; 1.92–3.23)</td>
<td>(0.09; 0.00–0.21)</td>
</tr>
<tr>
<td>Biliary system</td>
<td>2,330</td>
<td>89</td>
<td>(3.82; 3.03–4.61)</td>
<td>(0.82; 0.45–1.18)</td>
<td>(3.48; 2.72–4.23)</td>
<td>(0.04; 0.00–0.13)</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>1,086</td>
<td>23</td>
<td>(2.12; 1.25–2.98)</td>
<td>(0.74; 0.23–1.25)</td>
<td>(1.93; 1.11–2.76)</td>
<td>(0.18; 0.00–0.44)</td>
</tr>
<tr>
<td>Pancreas</td>
<td>3,445</td>
<td>124</td>
<td>(3.60; 2.97–4.23)</td>
<td>(0.73; 0.44–1.01)</td>
<td>(3.43; 2.81–4.04)</td>
<td>(0.18; 0.03–0.31)</td>
</tr>
<tr>
<td>p value</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data are number (%; 95% confidence interval) of patients.

Statistical Analysis

Statistical analysis was performed using StatView 5.0 (SAS Institute Inc, Cary, NC, USA). Comparisons of the incidence of PE according to tumor type and site were performed using the chi-square test. Data are presented as means with the 95% confidence interval (CI).

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tional cell carcinoma, squamous cell carcinoma, small cell carcinoma, large cell carcinoma, hepatic cell carcinoma, malignant lymphoma, myeloma and leukemia) and sites (lung, digestive system, liver, pancreas, biliary system, hematogenous tissue, kidney, urinary bladder, prostate, breast, uterus, ovary, thyroid and brain).
Results

A total of 1,708 patients with any type of PE were identified (2.62%; 95% CI, 2.50–2.74). The age distribution of this population is illustrated in Fig 1, with the peak incidence between ages 60 and 80 years.

The incidence of total PE was significantly associated with tumor site and histopathology (both, p<0.0001). Many cases of total PE occurred in patients with adenocarcinoma, leukemia and squamous cell carcinoma among the tumor types (digestive system and lung among the tumor sites) (Tables 1,2). The incidence of PE was high in leukemia, large cell carcinoma and adenocarcinoma (ovary, hematogenous tissue, biliary system, pancreas and lung among the sites), and low in hepatic cell carcinoma (liver and brain among the sites). Critical PE was found in 493 patients (0.76%; 95% CI 0.69–0.82), which comprised 28.9% of the total number of PE (493/1,708). Many cases of critical PE occurred with adenocarcinoma, among the tumor types, and in digestive system, lung and hematogenous tissue among the tumor sites. The incidence of critical PE was significantly associated with tumor type and site (p<0.0001). The incidence of critical PE was particularly high in leukemia and adenocarcinoma (ovary, hematogenous tissue and thyroid among the tumor sites), and less so in hepatic cell carcinoma and squamous cell carcinoma (liver among the tumor sites).

Thrombotic PE was identified in 1,514 patients (2.32%; 95% CI 2.21–2.44). The incidence was high in large cell carcinoma, leukemia and adenocarcinoma (ovary, hematogenous tissue, biliary system, pancreas and lung among the sites), and low in hepatic cell carcinoma (liver among the sites).

Tumor PE was identified in 124 patients (0.19%; 95% CI 0.16–0.22) and was particularly frequent in those with adenocarcinoma and hepatic cell carcinoma or when tumor was present in the digestive system and the liver. Tumor invasion into a large vein was identified in 69 patients (0.11%; 0.08–0.13). The incidence of this complication was high in those with hepatic cell carcinoma and when tumor was present in the liver and kidney. Nine of these 69 patients also had concomitant tumor PE.

Fig 2. Incidence of thrombotic pulmonary embolism (PE) and critical PE. (A) Incidence of thrombotic PE according to tumor type, (B) incidence of thrombotic PE according to tumor site, (C) incidence of critical PE according to tumor type, and (D) incidence of critical PE according to tumor site. Data are mean and 95% confidence interval (CI). (---) 95% CI of all patients with cancer.
Based on 10 histopathologic types of cancer, there was no significant correlation between the incidence of thrombotic PE and the incidence of tumor PE (r=0.21, p=0.57) or between the incidence of tumor PE and the incidence of tumor invasion into a large vein (r=0.51, p=0.13). Based on 14 primary sites of cancer, there was no correlation between the incidence of thrombotic PE and the incidence of tumor PE (r=0.06, p=0.83), but there was a significant correlation between the incidence of tumor PE and the incidence of tumor invasion into a large vein (r=0.71, p=0.004; Fig 3).

Discussion

Cancer and Thrombotic PE

In the present study, thrombotic PE was identified in 1,514 (2.32%) of 65,181 cancer patients, and thrombotic PE comprised 88.6% of all PE, including thrombotic PE, tumor PE, bacterial PE, mycotic PE and other emboli (eg, fat, amniotic fluid etc). This is consistent with widely reported data that cancer is associated with a hypercoagulable state that increases the risk of thromboembolic disease. Furthermore, the use of anticancer drugs can increase the risk of PE.

Previous studies have reported an overall incidence of PE in cancer patients of 1–15%. Coon et al reported that 17.1% of 1,394 patients with malignant conditions had thrombotic PE at autopsy, which is higher than the incidence of thrombotic PE in the present study. In another clinical study of 1,041 cancer patients, 81 patients (7.8%) were diagnosed with VTE, and the independent risk factors for PE included chemotherapy, advanced tumor, renal cell carcinoma, pancreatic carcinoma, gastric cancer and brain tumor. Because the incidence of PE is lower in non-black non-white Americans than in blacks or whites, the difference in the incidence of PE between these studies may be attributed to racial differences.

In the present study, PE was frequent in patients with adenocarcinoma and when tumor was present in the digestive system, lung and hematogenous tissue. Although malignant tumor is a risk factor for PE, it has been controversial whether we should aggressively investigate for malignant tumor in cases of primary PE. Sorensen et al. concluded that aggressive investigation into malignant tumor was not warranted.

Relationship Between Thrombotic PE, Tumor Histopathology and Tumor Site

The present study demonstrated that the incidence of thrombotic PE correlated with the tumor type and site. The incidence of thrombotic PE was high for adenocarcinoma, leukemia and large cell carcinoma, and low for hepatic cell carcinoma. Among the sites the incidence was high in hematogenous tissue, lung, ovary, biliary system and pancreas, and low in liver. Spoul et al previously reported the venous thrombosis was associated with carcinoma of the pancreas, particularly if the pancreatic body or tail was involved, but there are relatively few reports of venous thrombosis in patients in patients with carcinoma of the liver, which may reflect the high rate of concomitant cirrhosis in these patients, resulting in decreased prothrombin production. Indeed, one epidemiological study reported that liver disease reduces the odds ratio of PE.

Uderzo et al reported that 12 (2.7%) of 452 children with leukemia had PE and univariate analysis demonstrated a significant correlation between PE and acute myeloid leukemia. Furthermore, in a study of 719 adult patients with leukemia (534 acute myelogenous leukemia, 185 acute lymphoblastic leukemia), 15 patients (2.1%, of whom 5 patients had PE) had VTE, and VTE was found in all subtypes of acute leukemia, especially in patients with promyelocytic leukemia, a subtype of acute myelogenous leukemia. Finally, Kwaan et al reported that apoptotic acute promyelocytic leukemia cells produce higher levels of thrombin, which increases the risk of hypercoagulability and disseminated intravascular coagulation. These results are consistent with our result that PE is frequent in patients with leukemia.

The presence of a mucin-secreting adenocarcinoma of the digestive system and ovaries is also considered as a risk factor for secondary VTE. However, in the present study, this relationship did not reach statistical significance, possibly because of the low number of cases with mucinous carcinoma.

Tumor Embolism

In the present study, the incidence of tumor PE also correlated with tumor type and site. The incidence was higher for large cell carcinoma, hepatic cell carcinoma and adenocarcinoma among the tumor types, and higher in lung, ovary, kidney and liver among the tumor sites. Tumor PE and/or tumor invasion into a large vein was present in 193 patients (0.30%), which is less than that reported in previous studies. For example, the previous studies have reported that 2.4–26% of patients with solid malignant tumors had tumor embolization. Other studies have demonstrated that the risk of tumor embolization is increased by chemotherapy, radiation and surgical extirpation of the primary tumor, probably because these therapies promote fragmentation of the tumor mass and theoretically enhance tumor embolization via venous or lymphatic drainage.

Tumor PE can be classified into 2 different types according to the involvement of specific areas of the pulmonary vasculature. The first type involves either the main pulmonary arteries or the large segmental arteries. This type of emboli often can be diagnosed by pulmonary angiography, computed tomography or magnetic resonance angiography.
a macroscopic pulmonary tumor embolism. To distinguish tumor PE in proximal arteries from chronic thromboembolic pulmonary hypertension (CTEPH) is important because many cases of CTEPH have the indication of surgical therapy. The differentiation is, however, difficult before surgery or autopsy. The second type of tumor emboli involves the small arteries and/or arterioles, and is often difficult to diagnose correctly and may be considered as pulmonary hypertension of unknown cause antemortem. These microscopic pulmonary tumor embolism may be invisible on gross examination at autopsy. In the present study both of types were included.

Tamura et al reported that major tumor PE was present in 12 (3.8%) of 318 cancer patients at autopsy, including 6 patients with hepatic cell carcinoma and 3 patients with gastric cancer (adenocarcinoma). Moreover, macroscopic pulmonary tumor embolism was found in 6 patients, all of whom had hepatic cell carcinoma. Further, Ito et al reported that tumor PE was present in 18 patients (3.6%) of 500 cancer patients at autopsy, including 6 patients with sarcoma, 6 patients with hepatic cell carcinomas and 3 patients with renal cell carcinomas. In combination with results from the present study, these data suggest that tumor embolism occurs frequently with hepatic cell carcinoma.

On the other hand, Bassiri et al reported that in 30% of patients with tumor PE the primary site of the cancer was the breast, with lung cancer representing 9% and the prostate 7%. In their study the number of the patients according to the type of cancer was unknown, so the incidence of PE was not described. In most studies the described tumor PE has been limited to microscopic pulmonary tumor embolism, so we can not compare our data with those previously reported. Chan et al reported that hepatic cell carcinoma was the major cause of fatal tumor PE in oriental countries, but it is necessary to analyze this issue further.

Tumor Invasion Into a Large Vein

In the present study, the incidence of tumor invasion into a large vein was relatively high when there was tumor present in the liver or kidney. Furthermore, there was a significant correlation between the incidence of tumor PE and the incidence of tumor invasion into a large vein. This is consistent with the observation by Winterbauer et al that patients with hepatic cell carcinoma and major hepatic vein and inferior vena cava invasion had an increased incidence of tumor PE, and that in patients with renal cell carcinoma, tumor emboli were more frequent when the primary tumor invaded the renal vein and inferior vena cava. Moreover, according to their study, they noted that, despite a proclivity for major venous invasion 3-fold that seen in primary carcinoma of the liver, the incidence of tumor embolization was lower in patients with renal cell carcinoma than in those with hepatic cell carcinoma, suggesting that some factor related to tumor integrity or cohesiveness was operating in addition to the pattern of venous invasion in determining the incidence of tumor emboli.

**Study Limitations**

The first limitation of the present study is that it was based on previously published postmortem examinations. The affected site in the pulmonary vasculature was described in few patients with tumor PE. Therefore, we could not indicate the separate incidences of macroscopic and microscopic tumor PE. The second limitation is associated with the classification of the type of PE. Some cases had more than 1 type of PE (eg, thrombotic, tumor, septic etc). In cases in which 2 types of emboli were present, the patient was counted twice.

**Conclusion**

Thrombotic PE was found in 2.32% of all cancer patients at autopsy, which is a lower incidence than that found in previous studies. Furthermore, thrombotic PE comprised 88.6% of all cases of PE, including thrombotic PE, tumor PE, bacterial PE, mycotic PE and other emboli (eg, fat, amniotic fluid etc). Finally, the incidence of thrombotic PE, tumor PE and tumor invasion into a large vein was dependent on tumor type and site.

**Acknowledgment**

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**References**