Diseases of the Esophagus (2008) ••, ••–••
DOI: 10.1111/j.1442-2050.2008.00838.x

DISEASES OF THE ESOPHAGUS

Original article

High incidence of non-upper aerodigestive primary tumors in patients with esophageal cancer

R. Spector,[1] I. Liphshitz,[3] M. Barchana,[3,4] Y. Kundel,[2] N. Wasserberg,[1] S. Lelcuk,[1] A. Sulkes,[2] B. Brenner[2]

[1]Department of General Surgery and [2]Institute of Oncology, Davidoff Cancer Center, Rabin Medical Center, Beilinson Campus, Petah Tiqva, and Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv; the [3]Israeli National Cancer Registry, Ministry of Health, Jerusalem; and [4]the Israel School of Public Health, Haifa University, Haifa, Israel

SUMMARY. **Earlier reports have described an association between esophageal cancer (EC) and high incidence of other primary tumors (OPTs) of the upper aerodigestive tract and breast cancer. We evaluated the incidence of non-upper aerodigestive OPTs among Israeli EC patients; 2328 EC patients were retrieved from the Israeli National Cancer Registry between 1980 and 2004. The relative risk of OPTs for EC patients was measured using standardized incidence ratio (SIR). Two cohorts, Israeli National Cancer Registry registered colorectal cancer (CRC) patients and the general Israeli population, were used for reference; 297 EC patients (12.7%) had OPTs, including breast (18.9%), CRC (16.2%), prostate (8.8%), and bladder (8.4%) cancers. Upper aerodigestive OPTs were less common. Most OPTs were identified before (74.4%) or simultaneously with (13.8%) EC diagnosis. The median time interval between OPTs diagnoses and EC development was 6.0 years. The incidence of OPTs was significantly higher among EC patients compared with CRC patients (SIR: 2.05, $P < 0.01$) or the general Israeli population (SIR: 3.90, 95% CI: 3.46–4.34, $P < 0.01$) regardless of gender or tumor histology. Patients with EC have high incidence of non-upper aerodigestive malignancies. Unlike previous reports, the distribution of OPTs in EC seems to represent the relative incidences of these cancers in the western populations.**

KEY WORDS: **esophageal cancer, other primary tumors, upper aerodigestive tumors.**

INTRODUCTION

Esophageal cancer (EC) is the ninth most common malignancy and the sixth most frequent cause of cancer death, worldwide.[1] There are two main histological subtypes of EC: squamous cell carcinoma (SCC) and adenocarcinoma (ADC). Two decades ago, the large majority of these cancers were SCC, but since the early 1990s, ADC has become the most common histology of EC among white male patients in western countries.[2–4] The overall incidence of ADC of the esophagus in western countries accounts now for up to 50% of all esophageal cancers.[1]

The primary causes of SCC of the esophagus are tobacco use and alcohol consumption, whereas the main risk factors for ADC of the esophagus are gastroesophageal reflux disease and its sequelae, metaplasia of the chronically irritated epithelium known as Barrett's metaplasia, obesity, and tobacco smoking.[2,4–6]

It has been long acknowledged that there is a high incidence of other primary tumors (OPTs) of the upper aerodigestive tract among patients with EC, predominantly lung cancer, and head and neck cancers.[7–12] It was hypothesized that this association is caused by mutual carcinogens, such as tobacco and alcohol consumption.[7,13] There is also a documented connection between EC and prior breast cancer, which is mostly attributed to the carcinogenic effect of radiotherapy.[14] Earlier reports describe the occurrence of non-upper aerodigestive non-mammary

Address correspondence to: Dr Baruch Brenner, MD, Institute of Oncology, Davidoff Cancer Center, Rabin Medical Center, Beilinson Hospital, Petah Tiqva 49100, Israel. Email: brennerb@clalit.co.il

OPTs in patients with EC but the extent of this phenomenon is still unclear as of yet.[10–12,15,16]

The aim of the current study was to evaluate the actual incidence of non-upper aerodigestive OPTs among patients with EC in Israel. The source of information for this purpose was the database of the Israel National Cancer Registry (INCR).

MATERIALS AND METHODS

Patients

The database for this study was the INCR, a national population-based cancer registry that was established in 1960 and holds details regarding registration of all cancer patients.[17,18] This registry collects various data on cancer patients, such as age, gender, ethnicity, date of diagnosis, location and histology of tumors, and date of death. The INCR is a very reliable source of information because it has an over 95% report rate from 1980 onwards.[19]

We therefore studied the period 1980–2004, during which 2328 patients with EC were recorded in the database. Patients were eligible for this study if they had SCC or ADC in the upper, middle, or lower third of the esophagus. Tumors in the gastroesophageal junction (GEJ) were also included, but cardiac tumors were excluded, in order to avoid bias by misclassified gastric tumors.

Statistical analysis

The relative risk of OPTs for patients with EC was compared for a 25-year period, from 1980 to 2004, using standardized incidence ratios (SIR = observed cases/expected cases), and 95% confidence intervals (CI). *P* values of less than 5% were defined as statistically significant.

Expected cases for the observed group were calculated using incidence rates per 100 000 of reference groups for each gender and age group in the appropriate period.

As reference for comparison, two cohorts were chosen; one was made up of all patients with colorectal cancer (CRC) who were registered in the INCR and the second was the general Israeli population. The first cohort was selected in order to test the specific effect of EC as opposed to a general effect of any type of cancer. CRC was chosen due to its following features: it is a very common cancer globally and in Israel, it is not gender-specific, and it is relatively curable, permitting a follow up which is long enough to allow the development of other tumors. The comparison to the general Israeli population was done for purposes of validation.

Table 1 Clinicopathological characteristics of patients with esophageal cancer ($n = 2328$)

	n	%
Age (year)		
Median	72.1	
Range	52–84	
Gender		
Male	1388	59.6
Female	940	40.4
Ethnicity		
Arabs	53	2.3
Ashkenazi Jews	1433	61.5
Sepharadi Jews	556	23.9
Jews, ISR born	205	8.8
Unknown	81	3.5
Location of tumor		
Upper third	181	7.8
Middle third	243	10.4
Lower third	682	29.3
NOS	1222	52.5
Histology		
ADC	504	21.7
SCC	1293	55.5
NOS	531	22.8

ADC, adenocarcinoma; ISR, Israel; NOS, not otherwise specified; SCC, squamous cell carcinoma.

RESULTS

The clinicopathological characteristics of patients with EC that were included in this study are summarized in Table 1. The majority of tumors were located in the lower esophagus, yet over 70% of cases in which information on histology was available had SCC histology. Other patient's characteristics, including risk factors such as smoking, alcohol consumption, obesity, or family history, are not documented in the INCR registry. Of 2328 patients with EC, 297 (12.7%) were diagnosed with OPTs. The most common OPTs were breast cancer (18.9% of all cancers), CRC (16.2%), prostate (8.8%), and bladder (8.4%) cancers, making up more than half of all tumors (61%) (Fig. 1).

Upper aerodigestive OPTs were less common, with gastric, lung, and head and neck cancers, including larynx, comprising about 20% of all OPTs. When dividing the EC patients into two groups according to histology, ADC, or SCC, the distribution of the OPTs was similar, with the most common OPTs being breast, colorectal, and bladder or prostate cancer (Fig. 2).

As expected from the poor prognosis of EC, most of the OPTs were actually identified before (74.4%) or simultaneously with (13.8%) the EC. Only 11.8% were discovered after the diagnosis of EC. The median interval time between the diagnoses of OPTs to the subsequent development of EC was 6.0 years.

In comparison with the CRC cohort, the incidence of OPTs was significantly higher among patients with EC, with a SIR of 2.05 (95% CI: 1.81–2.28, $P < 0.01$). The statistical significance remained constant regard-

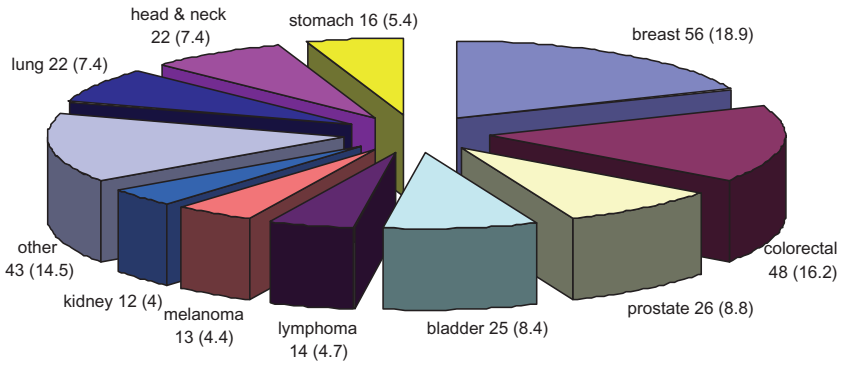

Fig. 1 Distribution of other primary tumors in patients with esophageal cancer ($n = 297$). Numbers in brackets represent percentage.

less of gender or histology of EC (Table 2). Our observation was more striking when the comparison was done with the Israeli general population cohort; patients with EC had almost a four-fold increased risk of developing another cancer as compared with the general risk in Israel to develop any type of cancer (SIR: 3.90, 95% CI: 3.46–4.34, $P < 0.01$). Again, this effect was independent of the gender of the EC patients or of their tumor histology (Table 3).

DISCUSSION

This study demonstrates a high incidence of OPTs in patients with EC as almost 13% of them were diagnosed with OPTs. The risk of OPTs in this population was double than that of patients with CRC and four times higher than the risk of the average Israeli population to develop cancer of any type. The results were consistent also when patients were stratified according to gender and histology. Considering the generally ominous outcome of EC, it is not surprising that most OPTs were diagnosed prior to the EC.

High incidence of OPTs in patients with EC has been reported before, mainly with regards to two tumor types: breast and upper aerodigestive cancers.[7–12,14,20] The high incidence of breast cancer was confirmed in our study but the incidence of upper aerodigestive OPTs, which have been reported to represent up to 70–90% of all OPTs in EC,[7,10–12]

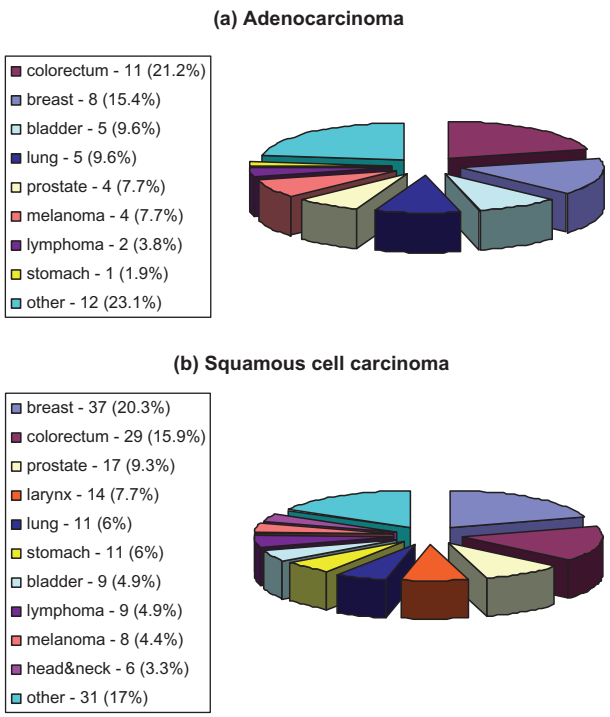

Fig. 2 Distribution of other primary tumors in patients with esophageal cancer according to histology: (a) adenocarcinoma ($n = 52$), (b) squamous cell carcinoma ($n = 182$).

Table 2 Risk of other primary tumors in patients with esophageal cancer versus patients with colorectal cancer

	Obs	Exp	SIR	CI	*P* value
Total	297	145.2	2.05	1.81–2.28	<0.01
Gender					
Male	178	88.88	2.00	1.71–2.30	<0.01
Female	119	56.32	2.11	1.73–2.49	<0.01
Histology					
SCC	182	93.26	1.95	1.67–2.24	<0.01
ADC	52	28.82	1.80	1.31–2.29	<0.01

ADC, adenocarcinoma; CI, 95% confidence interval; Exp, expected; Obs, observed; SCC, squamous cell carcinoma; SIR, standardized incidence ratios (Obs/Exp).

Table 3 Risk of other primary tumors in patients with esophageal cancer versus risk of cancer in the Israeli population

	Obs	Exp	SIR	CI	*P* value
General	297	76.18	3.9	3.46–4.34	<0.01
Gender					
Male	178	45.8	3.89	3.03–4.46	<0.01
Female	119	30.38	3.92	3.21–4.62	<0.01
Histology					
SCC	182	49.52	3.68	3.14–4.21	<0.01
ADC	52	13.83	3.76	2.74–4.78	<0.01

ADC, adenocarcinoma; CI, 95% confidence interval; Exp, expected; Obs, observed; SCC, squamous cell carcinoma; SIR, standardized incidence ratios (Obs/Exp).

was clearly lower than expected, with these tumors comprising only 20% of the OPTs we noted. In fact, the distribution of OPTs in our study resembled that of tumors in the general western population; more than 60% were made up of four leading tumors in this population: CRC, breast, prostate, and bladder cancers.[21] A recent report by Das *et al.*[16] based on the largest database ever studied on this topic, has also shown an increased risk of non-upper aerodigestive non-mammary OPTs in EC. However, the SIR of these tumors was in the order of 1.5–2, much lower than in our study, and the leading ones were cancers of the colon/rectum, pancreas, thyroid, and kidney. To put our results in perspective, data from several other studies and the current one are summarized in Table 4.

There are several possible explanations for the difference between our results and those of other reports. All of the studies, except that of Das *et al.*,[16] were much smaller than ours and were done exclusively on Asian patients and tumors with SCC histology.[7–12,14,20] The larger size of our study raises the possibility that its results reflect the actual phenomena more accurately. Nevertheless, our study was done on a different population and also included ADC, and hence, it may be that both our study and the earlier ones reflect the facts accurately but with regard to different patients and tumors.

The difference between our results and those reported by Das *et al.*[16] is more puzzling. Both studies are of a large size, both were done on western patients, and both included ADC and SCC histology, and in similar ratios. Still, in their study, Das *et al.*[16] noted a much lower SIR for OPTs, a difference between ADC and SCC, and a negative SIR for two of the leading OPTs in our study, bladder, and prostate cancers. Two main methodological differences may explain, at least in part, these discrepancies. First, Das *et al.*[16] evaluated OPTs which developed after the occurrence of EC. Considering the poor prognosis of EC, this markedly decreased the sample size and may have masked the real extent of the phenomenon. Second, Das *et al.*[16] used the Surveillance, Epidemiology and End Results (SEER) database. This database misses information on patients who moved to no-SEER areas and hence may be less accurate than the INCR database, which covers the entire Israeli population. Another possible cause for the different results is the similar yet not identical population studied. While both the American and Israeli populations are considered western, there are still some considerable differences in their actual ethnic composite and cultural habits.

If indeed there is a high rate of non-upper aerodigestive OPTs in patients with EC, its etiology is currently unknown. The development of EC following treatment for breast cancer is attributed to the radiotherapy, and perhaps chemotherapy, that are given for the latter.[14,22–24] This etiology seems not to apply to other non-upper aerodigestive cancers; chemotherapy regimens that are being used in CRC and bladder cancer are usually not carcinogenic, and radiotherapy for these diseases, or for prostate cancer, does not affect the thoracic or upper abdominal areas. As to carcinogenic effect of chemotherapy for prostate cancer, the use of chemotherapy in this disease is still limited. An increased rate of upper aerodigestive OPTs in EC has been explained by several factors: field cancerization phenomenon (i.e. mutual risk factors such as alcoholism and smoking), carcinogenic effect of radiotherapy used against some of these tumors, and hereditary factors that predispose individuals to multiple metaplasia.[7,13,15,20,25,26] None of these is relevant to the leading OPTs in our study. The fact that we did not identify one or two specific OPTs but rather a distribution that largely reflects the relative incidences of these tumors in western populations may provide a lead as to the pathogenesis of this phenomenon. Our results suggest that EC patients can be viewed as cancer-susceptible patients, i.e. patients who are prone to develop cancer more than the general population. According to our data, this risk is estimated to be a four-fold increase compared with the average risk, a hazard ratio that is similar to that reported before.[12] The fact that the histology of the EC did not alter the susceptibility for OPTs seems to support this perspective.

Table 4 Retrospective studies on the incidence of other primary tumors in patients with esophageal cancer

	Current study	Noguchi *et al.*[11]	Poon *et al.*[10]	Matsubara *et al.*[12]	Fogel *et al.*[7]	Das *et al.*[16]	
No. of patients with EC	2,328	421	1,055	679	198	10,467	14,804
Histology	ADC + SCC	SCC	SCC	SCC	SCC	ADC	SCC
Pts with OPTs (%)	297 (13)	92 (21)	100 (9.5)	254 (37)	24 (12.6)	NR	NR
No. of OPTs	297	92	114	320	24	287	690
Upper aerodigestive (%)	60 (20)	73 (86)	86 (75)	235 (73)	21 (87)	58 (20)	341 (49)
Non-aerodigestive (other than breast, %)	181 (61)	13 (14)	24 (21)	85 (26.5)	3 (12.5)	160 (56)	214 (31)
Breast (%)	56 (19)	0	4 (3.5)	NR	0	11 (4)	39 (5.5)
RR for OPTs	3.9	NR	NR	2.98	NR	1.34	2.29

ADC, adenocarcinoma; EC, esophageal cancer; NR, not reported; OPTs, other primary tumors, Pts, patients; RR, relative risk; SCC, squamous cell carcinoma.

The conditions and processes that underlie this general propensity for cancer, whether genetic or immunologic, are clearly very important for the development of EC. These factors are currently unknown but their identification may provide crucial information not only on the pathogenesis of EC but also on the basic processes that promote carcinogenesis.

In conclusion, the current study demonstrates that patients with EC have a high incidence of non-upper aerodigestive tumors. The distribution of these tumors parallels their prevalence in western populations. As the OPTs usually precede the EC, our findings suggest a need for an early evaluation of any cancer patient who develops symptoms which may be EC-related.

References

1 Kuwano H, Kato H, Miyazaki T *et al*. Genetic alteration in esophageal cancer. Surg Today 2005; 35: 7–18.
2 Blot W J, McLaughlin J K. The changing epidemiology of esophageal cancer. Semin Oncol 1999; 26: 2–8.
3 Gamliel Z. Incidence, epidemiology and etiology of esophageal cancer. Chest Clin North Am 2000; 10: 441–50.
4 Crew K D, Neugut A I. Epidemiology of upper gastrointestinal malignancies. Semin Oncol 2004; 31: 450–64.
5 Blot W J, Devesa S S, Kneller R W, Fraumeni J F. Rising incidence of adenocarcinoma of the esophagus and gastric cardia. JAMA 1991; 265: 1987–9.
6 Pera M, Manterola C, Vidal O, Grande L. Epidemiology of esophageal adenocarcinoma. J Surg Oncol 2005; 92: 151–9.
7 Fogel T D, Harisson L B, Son Y H. Subsequent upper aerodigestive malignancies following treatment of esophageal cancer. Cancer 1985; 55: 1882–5.
8 Shibuya H, Wakita T, Nakagawa T, Fukuda H, Yasumoto M. The relation between an esophageal cancer and associated cancers in adjacent organs. Cancer 1995; 76: 101–5.
9 Hsieh W C, Chen Y M, Perng R P. Temporal relationship between cancers of the lung and upper aerodigestive tract. Jpn J Clin Oncol 1997; 27: 63–6.
10 Poon R T P, Law S Y K, Chu K-M, Branicki F J, Wong J. Multiple primary cancers in esophageal squamous cell carcinoma: incidence and implications. Ann Thorac Surg 1998; 65: 1529–34.
11 Noguchi T, Kato T, Takeno S, Wada S, Yanagisawa S, Suzuki M. Necessity of screening for multiple primary cancers in patients with esophageal cancer. Ann Thorac Cardiovasc Surg 2002; 8: 336–42.
12 Matsubara T, Yamada K, Nakagawa A. Risk of second primary malignancy after esophagectomy for squamous cell carcinoma of the thoracic esophagus. J Clin Oncol 2003; 21: 4336–41.
13 Licciardello J T W, Spitz M R, Hong W K. Multiple primary cancer in patients with cancer of the head and neck, second cancer of the head and neck, esophagus and lung. Int J Radiat Oncol Biol Phys 1989; 17: 467–76.
14 Roychouduri R, Evans H, Robinson D, Moller H. Radiation-induced malignancies following radiotherapy for breast cancer. Br J Cancer 2004; 91: 868–72.
15 Takahashi K, Yoshida H, Mamada Y *et al*. Case report of metachronous hepatocellular carcinoma and early esophageal cancer. J Nippon Med Sch 2005; 72: 187–90.
16 Das A, Thomas S, Zablotska L B *et al*. Association of esophageal adenocarcinoma with other subsequent primary cancers. J Clin Gastroenterol 2006; 40: 405–11.
17 Barchana M, Liphshitz I, Rozen P. Trends in colorectal cancer incidence and mortality in the Israeli Jewish ethnic populations. Familial Cancer 2004; 3 (3–4): 207–14.
18 Freedman L S, Edwards B K, Ries L A G, Young J L (eds). Cancer Incidence in Four Member Countries (Cyprus, Egypt, Israel, and Jordan) of the Middle East Cancer Consortium (MECC) compared with US SEER. Bethesda, MD: National Cancer Institute, 2006; NIH Publication No. 06-5873.
19 The National Center for Disease Control. Examination of Israel national cancer data accumulation completeness for 1991. Haifa, Israel: Carmel Medical Center, 2003; Publication No. 230.
20 Begg C B, Zhang Z, Sun M, Herr H W, Schantz S P. Methodology for evaluating the incidence of second primary cancers with application to smoking-related cancers from the surveillance, epidemiology, and end results (SEER) program. Am J Epidemiol 1995; 142: 653–65.
21 Parkin D M, Bray F, Ferlay J, Pisani P. Global Cancer Statistics, 2002. CA Cancer J Clin 2005; 55: 74–108.
22 Hashibe M, Ritz B, Le A D, Li G, Sankaranarayanan R, Zhang Z F. Radiotherapy for oral cancer as a risk factor for second primary cancers. Cancer Lett 2005; 220: 185–95.
23 Levi F, Randimbison L, Te V C, La Vecchia C. Increased risk of esophageal cancer after breast cancer. Ann Oncol 2005; 16: 1829–31.
24 Zablotska L B, Chak A, Das A, Neught A I. Increased risk of squamous cell esophageal cancer after adjuvant radiation therapy for primary breast cancer. Am J Epidemiol 2005; 161: 330–7.
25 Wynder E L, Mushinski M H, Spivak J C. Tobacco and alcohol consumption in relation to the development of multiple primary cancers. Cancer 1997; 40: 1872–8.
26 Van Oijen M G, Slootweg P J. Oral field cancerization: carcinogen-induced independent events or micrometastatic deposits? Cancer Epidemiol Biomarkers Prev 2000; 9: 249–56.