mutation, uncommon in gastric cancer, is deleterious for p53 protein function, encoding for an altered and non-functional isoform [12,13]. Interestingly from a clinical point of view, β-sandwich mutations, such as p.V143A c.428T>C, are considered very promising targets for functional p53 rescue by generic small molecule drugs, able to restore wild-type-like activity [13]. When both alleles encode for a non-functional protein, p53 loses its function of 'guardian of the genome', causing high genomic instability and resistance to anticancer drugs [12]. In our case, homozygosity for p.V143A (c.428T>C) mutation could have caused tumor resistance after a prolonged response to trastuzumab.

Due to the small size of the liver lesion and the ethical problem of performing a 'clinically not required' liver biopsy, it has not been possible to analyze the liver metastasis upfront treatment with trastuzumab. Missing this initial analysis, another hypothesis for the acquired resistance to trastuzumab could be that the mutation already existed when the metastasis first appeared, representing a more malignant subclone from the primary tumor. As regards to the expression of p53, IHC staining is usually used as a surrogate for mutational analysis in the diagnostic workup of carcinomas of multiple sites, a strong and diffuse pattern of p53 expression (greater than 60% of cells) being associated with a mutated TP53 gene in the most of cases [14]. In our case, IHC was not able to discriminate the heterozygous mutation of TP53 in the primary tumor and the homozygous mutation in the metastatic lesion, both appearing intensely positive.

In conclusion, in our case, homozygosity for p.V143A c.428T>C mutation in exon5 of TP53 gene could be the cause of the acquired resistance in the course of trastuzumab therapy. Considering the difficulty to find suitable metastatic tissue specimens for molecular assessments and the uncommon presence of this mutation in gastric cancer, it could be hard to clinically verify this hypothesis, which, in our opinion, could be otherwise tested in vitro on HER2 overexpressing gastric cancer cell lines transfected with the p.V143A c.428T>C mutation.

Acknowledgement

Current Research Number 08067611 IRCCS Policlinico San Matteo Foundation

References

1. Bang YJ, Van Cutsem E, Feyereislova A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. Lancet 2010;376:687–97.
2. Grimes N, Devlin J, Dunne DF, et al. The role of hepatectomy in the management of metastatic gastric adenocarcinoma: a systematic review. Eur J Surg Oncol 2014;23:177–85.
3. Thery JC, Spano JP, Azria D, et al. Resistance to human epidermal growth factor receptor type 2-targeted therapies. Eur J Cancer 2014;50:892–901.
4. Lee HE, Park KU, Yoo SB, et al. Clinical significance of intratumoral HER2 heterogeneity in gastric cancer. Eur J Cancer 2012;49:1448–57.
5. Gomez-Martin C, Plaza JC, Pazo-Cid R, et al. Level of HER2 gene amplification predicts response and overall survival in HER2-positive advanced gastric cancer treated with trastuzumab. J Clin Oncol 2013;31:4445–52.
6. Ebbing EA, Medema JP, Damhofer H, et al. ADAM10-mediated release of heregulin confers resistance to trastuzumab by activating HER3. Oncotarget 2016;7:10243–54.
7. Arienti C, Zanoni M, Pignatta S, et al. Preclinical evidence of multiple mechanisms underlying trastuzumab resistance in gastric cancer. Oncotarget 2016;7:18424–39.
8. Lu Y, Zi X, Zhao Y, et al. Insulin-like growth factor-I receptor signaling and resistance to trastuzumab. (Herceptin). J Natl Cancer Inst 2001;93:1852–7.
9. Casalini P, Botta L, Menard S. Role of p53 in HER2-induced proliferation or apoptosis. J Biol Chem 2001;276:12449–53.
10. Housman G, Byler S, Heerboth S, et al. Drug resistance in cancer: an overview. Cancers 2014;6:1769–92.
11. Chen H, Ye Q, Lv J, et al. Evaluation of trastuzumab anti-tumor efficacy and its correlation with HER2 status in patient-derived gastric adenocarcinoma xenograft models. Pathol Oncol Res 2015;21:947–55.
12. Petitjean A, Mathe E, Kato S, et al. Impact of mutant p53 functional properties on TP53 mutation patterns and tumor phenotype: lessons from recent developments in the IARC TP53 database. Hum Mutat 2007;28:622–9.
13. Joerger AC, Ching Ang H, Fersht AR. Structural basis for understanding oncogenic p53 mutations and designing rescue drugs. Proc Natl Acad Sci USA 2006;103:15056–61.
14. Yemelyanova A, Vang R, Kshirsagar M, et al. Immunohistochemical staining patterns of p53 can serve as a surrogate markers for TP53 mutations in ovarian carcinoma: an immunohistochemical and nucleotide sequencing analysis. Modern Pathol 2011;24:1248–53.

LETTER TO THE EDITOR

The risk of secondary primary malignancy in early stage differentiated thyroid cancer: a US population-based study

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ARTICLE HISTORY Received 11 May 2016; revised 22 May 2016; accepted 24 May 2016

Thyroid cancer is the most rapidly increasing cancer in the US. Its incidence has nearly tripled from 4.9 to 14.3 per 100 000 individuals over the last three decades [1]. It is commonly diagnosed at a younger age group as compared to other adults' cancers [2]. The American Cancer Society estimated about 62 450 new cases of thyroid cancer will be diagnosed in the US in the year 2016 [2].

Papillary and follicular thyroid cancers are referred to as differentiated thyroid cancers. They account for more than 90% of all the thyroid cancers [3]. By 2019, papillary thyroid cancer alone will become the third most common cancer in women of all ages [4].

The patients with differentiated thyroid cancer are often treated similarly. Also, patients with early stage differentiated thyroid cancers (follicular and papillary) have excellent long-term survival [5,6]. The risk of second primary malignancy (SPM) has become a significant concern among these cancer survivors. In this study, we aim to identify the risk of SPM after a diagnosis of stage I (T1a) differentiated thyroid cancer.

Method

We utilized Surveillance, Epidemiology and End Results (SEER)-13 registry to select adult patients ($\geq$18 years of age) diagnosed with stage I (T1a) follicular or papillary thyroid cancer as their first malignancy between January 2004 and December 2010. SEER database of the National Cancer Institute is a population-based database that assembles data related to incidence and survival on cancer patients in the US. It is a useful tool to view individual cancer records and to produce statistics for studying the impact of cancer on a population. It covers approximately 30% of the US population [7]. SEER 13 registries consist of Atlanta, Connecticut, Detroit, Hawaii, Iowa, New Mexico, San Francisco-Oakland, Seattle-Puget Sound, Utah, Los Angeles, San Jose-Monterey, Rural Georgia and the Alaska Native Tumor Registry.

SPM is defined as a metachronous cancer which develops $\geq$6 months after an index thyroid cancer based on Warren and Gates criteria. We obtained multiple primary standardized incidence ratio (MP-SIR) and an absolute excess risk (AER) for an occurrence of SPM using SEER stat program. SIR is ratio of observed to expect incidence ratio (O/E) of SPM and AER is the actual number of excess SPMs in patient with index thyroid cancer per 10 000 person-years at risk. Statistical significance was defined for a p-value $\leq$0.05.

Results

The database included a cohort of 12 603 patients during this time frame. The median follow-up duration was 154 months (9–251 months). A total of 1246 (9.8%) patients developed 1389 SPMs with an O/E of 1.2 (95% CI 1.14–1.27, $p < 0.0001$) and an AER of 16.23 per 10 000 patient population. The median age at diagnosis of SPM was 66 years (range 19–99 years). The median latency for the first SPM was 86 months (6–239 months). The demographics of this study are summarized in Table 1.

A significant excess risk was observed for malignancies of salivary gland (O/E = 2.8, CI 1.91–6.84, $p < 0.001$), melanoma of the skin (O/E = 1.6, CI 1.31–2.08, $p < 0.001$), female breast (O/E = 1.19, CI 1.06–1.34, $p < 0.0001$), ovary (O/E = 1.45, CI 1.02–2.01, $p < 0.0001$), male genital system (O/E = 1.26, CI 1.07–1.48, $p < 0.005$), urinary system (O/E = 1.84, CI 1.55–2.17, $p < 0.0001$) and lymphatic and hematopoietic system (O/E = 1.24, CI 1.02–1.48, $p < 0.02$). An increased risk for large intestine cancer was significant within 24 months, whereas the risk for salivary gland, bones and joints, female breast, prostate, testicular and hematopoietic malignancies were significant after 24 months of diagnosis of primary cancer. Likewise, an increased risk for the liver and hematopoietic malignancies were significant in the younger (<60 years) patients whereas the risk of bones and joints, prostate and urinary bladder cancers were significant in older patients. These findings are summarized in Table 2.

Discussion

Our study suggests that the survival of differentiated thyroid cancer patients are at increased risk of developing SPMs than the general population. They are at increased risk of developing malignancies of salivary gland, melanoma, female breast, male genital system, ovary, urinary system, lymphatic and hematopoietic system, etc. This risk has been demonstrated in different clinical studies [8–11]. To our knowledge, this is the first and the largest population-based study to demonstrate this finding in the US.

This increased risk might either be related to patient- or tumor-specific characteristic. An excess risk has also been related to radioiodine therapy [8]. Sawka et al. demonstrated a slightly increased risk of SPMs in patients treated with radioactive iodine [10]. However, Fallahi et al. suggested an increased activity might be related to cumulative activity of I-131 [11]. We therefore recommend further study to verify this finding.

Table 1. Demographics of our study.

Demographics	N	Percentage
Total number of patients	12 603	
Gender		
Male	3091	24.5
Female	9512	75.5
Race		
Caucasian	10 422	82.7
African American	584	4.6
Other	1595	12.7
Total SPM	1389	
Total patient with SPM	1246	9.8 (of thyroid cancer patients)
• Total number of patients with one SPM	1121	89.97
• Total number of patients with 2 or more SPM	125	10.03

N: sample size; SPM: second primary malignancy.

Table 2. Second primary malignancy in thyroid cancer.

	N	O/E	Two-tailed p-value	CI	AER
All sites	1389	1.2	<0.001	1.14–1.27	16.23
All sites excluding non-melanoma skin	1382	1.2	<0.001	1.14–1.27	16.05
All solid tumors	1244	1.21	<0.001	1.14–1.27	14.55
Salivary gland	11	3.82	<0.001	1.91–6.84	0.56
Bones and joints	7	5.05	0.001	2.03–10.4	0.39
Skin excluding basal and squamous	85	1.66	<0.001	1.32–2.05	2.31
Melanoma of the skin	78	1.66	<0.001	1.31–2.08	2.14
Breast	292	1.19	0.004	1.06–1.34	3.22
Female breast	291	1.19	0.004	1.06–1.34	3.21
Ovary	36	1.45	0.041	1.02–2.01	0.77
Male genital system	156	1.26	0.006	1.07–1.48	2.22
Prostate	149	1.23	0.016	1.04–1.44	1.91
Testis	6	3.48	0.017	1.28–7.57	0.29
Urinary system	142	1.84	<0.001	1.55–2.17	4.45
Urinary bladder	69	1.55	0.001	1.21–1.96	1.68
Kidney and renal pelvis	65	2.12	<0.001	1.64–2.71	2.36
Renal pelvis, ureter and other urinary organs	15	3.5	<0.001	1.96–5.77	0.74
Kidney	58	2.04	<0.001	1.55–2.64	2.04
Renal pelvis	7	3.12	0.016	1.25–6.43	0.33
Ureter	6	4.48	0.005	1.65–9.76	0.32
Endocrine system	44	1.41	0.036	1.02–1.89	0.88
Other endocrine	2	10.88	0.029	1.32–39.32	0.12
All lymphatic and hematopoietic diseases	116	1.24	0.029	1.02–1.48	1.53
Leukemia	46	1.64	0.002	1.2–2.19	1.24
Acute lymphocytic leukemia	6	4.53	0.005	1.66–9.86	0.32
Non-lymphocytic leukemia	28	1.92	0.002	1.27–2.77	0.92
Acute non-lymphocytic leukemia (ANLL)	22	2.27	0.001	1.42–3.44	0.85
Myeloid and monocytic leukemia	27	2.07	0.001	1.36–3.01	0.96
Acute myeloid leukemia	21	2.48	<0.001	1.53–3.79	0.86

AER: absolute excess risk; CI: confidence interval; N: sample size; O/E: observed/expected ratio.

Differentiated thyroid cancer is one of most common endocrine malignancies. The incidence rate of which has increased significantly in last three decades [12]. Patients with differentiated thyroid cancers have an excellent survival with 10-year survival rate ranging from 80% to 95% [13]. This suggests that the course of the disease is very trivial and these people live longer. The impact of thyroid cancer on society has never been significantly appreciated. Aschebrook-Kilfoy et al. suggested a total cost of $2.38 billion (or $3.1 billion unadjusted) for 2019 [4]. It is true that most people survive thyroid cancer, but at the same time they might develop severe complications from other malignancies if not treated at the right time. An increase in awareness among survivors and regular follow-up with close surveillance for SPM might improve the survival rate and further decrease the economic burden. A detailed history and thorough physical examination can provide valuable information before choosing any diagnostic imaging modality during the surveillance visit. This will definitely decrease the cost burden and unnecessary exposure to radiation.

SEER database covers a large population sample which is comparable to the general US population with regards to measures of poverty and education [14]. This largely representative population sample, long follow-up period and huge sample size are the major strengths of our study. However, SEER program does not have individual patient information including a patient's risk factor, family history of other cancers, socioeconomic status, comorbidities and exposure to carcinogens. This is one of the major limitations of our study.

In conclusion, our study showed an increased risk of SPM in patients with thyroid cancer. We therefore recommend a regular follow-up with special focus on cancer-specific screening in these survivors.

Disclosure statement

The authors declare that they have no conflict of interests.

References

1. Davies L, Welch HG. Current thyroid cancer trends in the United States. JAMA Otolaryngol Head Neck Surg 2014;140:317–22.
2. American Cancer society. Available URL: http://www.cancer.org/cancer/thyroidcancer/detailedguide/thyroid-cancer-key-statistics (last accessed at May 1, 2016).
3. Aschebrook-Kilfoy B, Ward MH, Sabra MM, et al Thyroid cancer incidence patterns in the United States by histologic type, 1992–2006. Thyroid 2011;21:125–34.
4. Aschebrook-Kilfoy B, Schechter RB, Shih YC, et al. The clinical and economic burden of a sustained increase in thyroid cancer incidence. Cancer Epidemiol Biomarkers Prev 2013;22:1252–9.
5. Shaha AR, Shah JP, Loree TR. Low-risk differentiated thyroid cancer: the need for selective treatment. Ann Surg Oncol 1997;4:328–33.
6. Shah JP, Loree TR, Dharker D, et al. Prognostic factors in differentiated carcinoma of the thyroid gland. Am J Surg 1992;164:658–61.
7. National Cancer Institute Surveillance, Epidemiology, and End Results Program. Overview of the SEER program. Available URL: http://seer.cancer.gov/about/overview.html (last accessed at May 1, 2016).
8. Lang BH, Wong IO, Wong KP, et al. Risk of second primary malignancy in differentiated thyroid carcinoma treated with radioactive iodine therapy. Surgery 2012;151:844–50.
9. Berthe E, Henry-Amar M, Michels JJ, et al. Risk of second primary cancer following differentiated thyroid cancer. Eur J Nucl Med Mol Imaging 2004;31:685–91.
10. Sawka AM, Thabane L, Parlea L, et al. Second primary malignancy risk after radioactive iodine treatment for thyroid cancer: a systematic review and meta-analysis. Thyroid 2009;19:451–7.
11. Fallahi B, Adabi K, Majidi M, et al. Incidence of second primary malignancies during a long-term surveillance of patients with differentiated thyroid carcinoma in relation to radioiodine treatment. Clin Nucl Med 2011;36:277–82.
12. Chen AY, Jemal A, Ward EM. Increasing incidence of differentiated thyroid cancer in the United States, 1988–2005. Cancer 2009;115:3801–7.
13. Links TP, van Tol KM, Jager PL, et al. Life expectancy in differentiated thyroid cancer: a novel approach to survival analysis. Endocr Relat Cancer 2005;12:273–80.
14. National Cancer Institute Surveillance. Epidemiology, and End Results Program, Cancer statistics. Available URL: http://seer.cancer.gov/registries/characteristics.html (last accessed at March 5, 2016).